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Concise International Chemical Assessment Document 56

1,2,3-TRICHLOROPROPANE

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all

possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.¹

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that

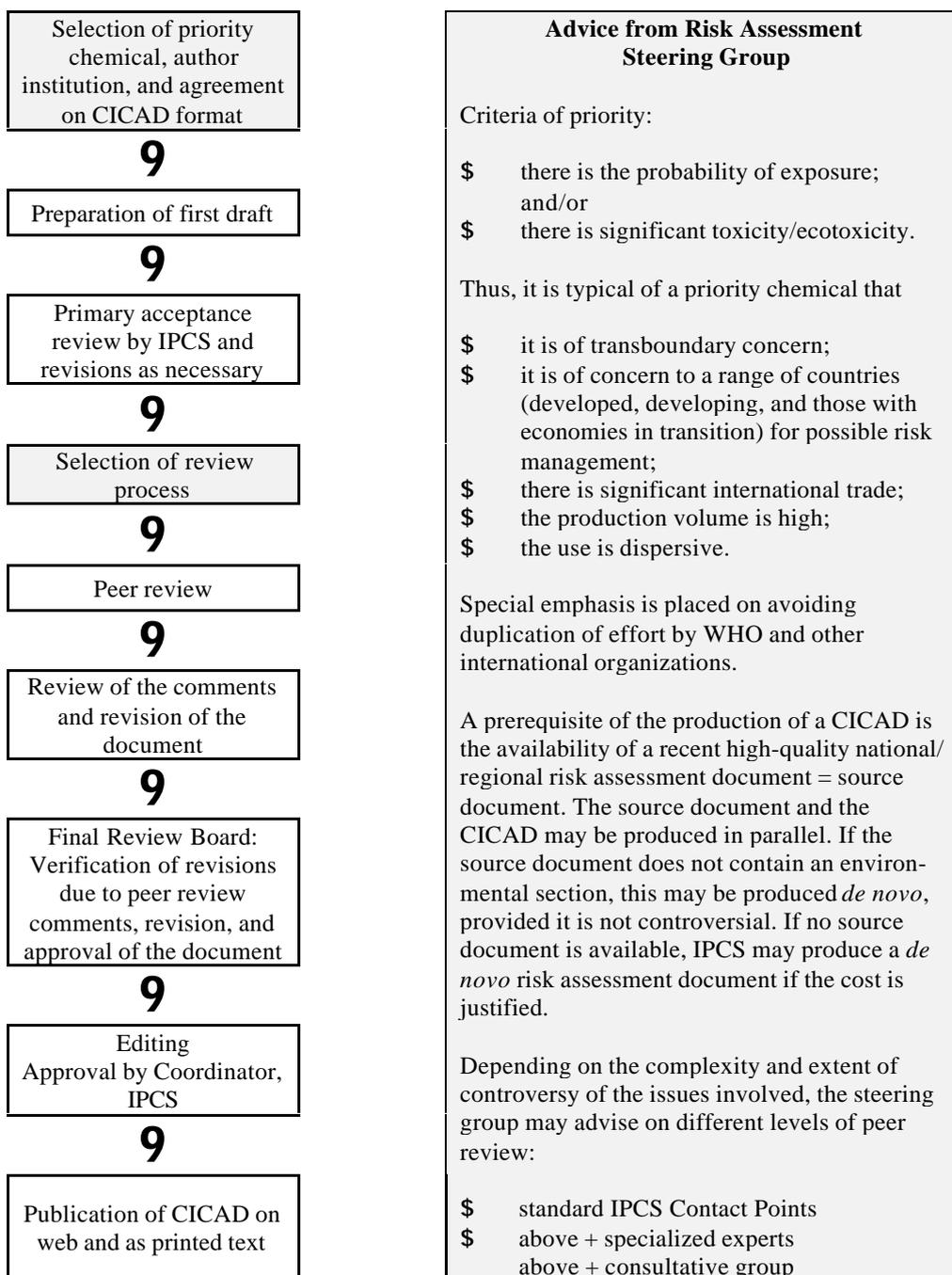
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e., EHC or CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170) (also available at <http://www.who.int/pcs/>).

CICAD PREPARATION FLOW CHART



The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on 1,2,3-trichloropropane was prepared by the Fraunhofer Institute of Toxicology and Aerosol Research, Drug Research and Clinical Inhalation, Hanover, Germany. It is based on reports compiled by the German Advisory Committee on Existing Chemicals of Environmental Relevance (BUA, 1993) and the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK, 1993). A comprehensive literature search of relevant databases was conducted in November 2001 for health effects and in September 2002 for environmental effects to identify any relevant references published subsequent to those incorporated in these reports. Information on the preparation and peer review of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Monks Wood, United Kingdom, on 16–19 September 2002. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for 1,2,3-trichloropropane (ICSC 0683), produced by the International Programme on Chemical Safety (IPCS, 1999), has also been reproduced in this document.

1,2,3-Trichloropropane (CAS No. 96-18-4) is a chlorinated alkane. Not only is it manufactured itself, but it is produced in significant quantities as a by-product of the production of other chlorinated compounds, including epichlorohydrin. It is used as an intermediate in the synthesis of other chemicals (e.g., pesticides) and as a crosslinking agent in the production of polymers, such as polysulfides and hexafluoropropylene. In older reports, 1,2,3-trichloropropane was identified as a solvent for hydrophobic compounds and resins, as a paint and varnish remover, and as a degreasing agent.

The predominant target compartment for 1,2,3-trichloropropane in the environment is air (about 85%), followed by water (about 11%). Reported concentrations of 1,2,3-trichloropropane in ambient air in the USA and Europe range from not detected to 0.4 µg/m³. In European rivers, concentrations range from not detected to 2.2 µg/litre.

1,2,3-Trichloropropane released into the environment is only poorly converted by abiotic processes (e.g., transformation by photochemically produced hydroxyl radicals) and might therefore remain present for extended periods. However, it can be removed from aquatic systems by evaporation and might be leached from soil into groundwater, due to the low soil sorption coefficients (K_{oc}) reported for this compound. It is not readily biodegraded and is only slowly transformed by

bacteria under aerobic and anaerobic conditions. The data available on the bioconcentration of this chlorinated alkane indicate that it is unlikely to bioaccumulate.

The main routes of exposure to 1,2,3-trichloropropane are via inhalation of contaminated air and ingestion of contaminated drinking-water. The chemical can be absorbed dermally to a more limited extent.

In animal studies, 1,2,3-trichloropropane is rapidly absorbed from the gastrointestinal tract, metabolized, and excreted. Orally applied doses were excreted within 60 h via urine (50–65%), faeces (15–20%), and breath as carbon dioxide (20%). 1,2,3-Trichloropropane appears to be metabolized faster in mice than in rats.

In rats, after oral administration, the major urinary metabolite (40% of urinary radioactivity) identified after 6 h is a mercapturic acid conjugate, *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-*L*-cysteine. In the 24-h urine, a second metabolite, a cysteine conjugate (*S*-(3-chloro-2-hydroxypropyl)-*L*-cysteine), was determined. ¹⁴C activity in target organs (i.e., liver, kidney, and fore-stomach) was still found 60 h after oral administration of [¹⁴C]1,2,3-trichloropropane. After intravenous injection of 1,2,3-trichloropropane to rats, one major metabolite in the bile was 2-(*S*-glutathionyl)malonic acid. In mice, the urinary metabolite spectrum is more complex.

The isolation of the above metabolites suggests that biotransformation of 1,2,3-trichloropropane involves both conjugation with glutathione (GSH) and oxidation. One proposed pathway in the liver is the mixed-function oxidase-catalysed oxygenation of 1,2,3-trichloropropane on a terminal carbon to yield a chlorohydrin, followed by additional reactions that result in formation of the observed metabolites. A second pathway in the liver may involve the GSH transferase-catalysed formation of GSH conjugates, which either undergo additional biotransformation in the liver or are excreted in bile or plasma.

1,2,3-Trichloropropane is of moderate acute toxicity, with oral LD₅₀ values in the rat ranging from 150 to 500 mg/kg body weight. Dermal toxicity is lower, with reported LD₅₀ values of 836 mg/kg body weight in a single rat study and values ranging from 384 to 2457 mg/kg body weight in rabbits. A 4-h LC₅₀ of about 3000 mg 1,2,3-trichloropropane/m³ was determined for rats and mice. The prominent toxic effect is irritation of the mucosa of eyes and nose and liver and kidney damage.

1,2,3-Trichloropropane is an irritant to skin and mucous membranes. In various tests with guinea-pigs, 1,2,3-trichloropropane showed no or only a very slight sensitizing effect.

The primary effect of repeated exposure of F344 rats and B6C3F1 mice to up to 780 mg 1,2,3-trichloropropane/m³ for 9 days by inhalation was a microscopic degenerative and inflammatory change in the nasal olfactory mucosa. In mice, testes weights were significantly reduced at the highest dose, but without associated histopathological changes. There were no other findings except for changes in liver weight in the highest dose group. In a repeated-dose experiment with doses up to 61 mg/m³, the overall no-observed-adverse-effect level (NOAEL) was 6 mg/m³ for rats and 18 mg/m³ for mice for changes in the olfactory epithelium detectable by histopathological examination.

In another study in which CD rats were exposed to up to 300 mg/m³ for 13 weeks, toxic effects in the upper respiratory tract, lung, and liver were observed. A follow-up study with doses up to 9.2 mg/m³ reported signs of irritation of mucous membranes (increase of lacrimal discharge), even at the lowest concentration of 3.1 mg/m³. The only systemic effects were changes in haematological parameters and increases in lung and ovary weights without corresponding microscopic findings.

After medium-term oral exposure of F344 rats to 1,2,3-trichloropropane, the principal toxic lesions occurred in liver, kidney, and nasal turbinates, with males showing a greater sensitivity. Haematological changes at 16 mg/kg body weight per day and higher dosages were interpreted as non-regenerative anaemia, possibly associated with a depression in erythropoiesis. The lowest-observed-adverse-effect level (LOAEL) for a 17-week treatment by gavage was 8 mg/kg body weight per day in male rats and 16 mg/kg body weight per day in female rats (increase in absolute liver weight). In B6C3F1 mice, the main targets of toxic action were lung, liver, and forestomach. Mice tolerated higher doses than rats, with LOAELs (hyperplasia of bronchiolar epithelium and hyperplasia and hyperkeratosis of forestomach) of 63 mg/kg body weight per day in female mice and 125 mg/kg body weight per day in male mice. A cardiotoxic effect discussed by one working group was not confirmed by these studies, which covered comparable or longer treatment periods. Gavage as a bolus application produced more severe effects than continuous application via drinking-water at a comparable dose level. When 1,2,3-trichloropropane was administered to Sprague-Dawley rats via drinking-water for 13 weeks, the LOAELs for increased relative liver and kidney weights were 17.6 mg/kg body weight per day for female rats and 113 mg/kg body weight per day for male rats.

From a variety of *in vitro* genotoxicity tests (e.g., gene mutations in bacterial and mammalian cells, gene conversions in *Saccharomyces cerevisiae*, induction of

sister chromatid exchange, chromosomal aberrations, and micronuclei), a genotoxic potential of 1,2,3-trichloropropane in the presence of metabolic activation systems is evident. Single data on a direct genotoxic action of 1,2,3-trichloropropane seem questionable. *In vivo*, DNA single strand breaks were detectable by alkaline elution, whereas genotoxic action in a dominant lethal test was absent.

The major DNA adduct, S-[1-(hydroxymethyl)-2-(N⁷-guanylyl)ethyl]glutathione, and other DNA adducts were identified in preneoplastic and neoplastic lesions of target organs.

The results of a two-generation study in Swiss mice showed that 1,2,3-trichloropropane impaired fertility and reproduction at a dose level of 120 mg/kg body weight per day (administered via gavage) in both the parent and the offspring generations in the presence of only slight systemic toxicity. A cross-mating trial suggested greater toxicity for the female than for the male reproductive system. The average estrous cycle length was significantly increased for all 1,2,3-trichloropropane-exposed females of the F₁ generation, with the lowest dose being 30 mg/kg body weight per day.

1,2,3-Trichloropropane is a multisite carcinogen with corresponding preneoplastic lesions in both rats and mice after long-term application by gavage. Main targets of carcinogenic action are the forestomach and the oral mucosa in rats of both sexes, the mammary gland in female rats, pancreas and kidney in male rats, as well as preputial gland and clitoral gland, as homologous organs in male and female rats, respectively. Mice responded with neoplasms of the forestomach, the liver, and the Harderian gland. Uncommon tumour types were reported, such as carcinomas of the Zymbal's gland and adenomatous polyps or adenocarcinomas of the intestine in rats and uterine neoplasms in mice. Considering the very high incidences of forestomach neoplasms in low-dose groups of rats (33–66%) and mice (nearly 100%), this carcinogenic activity might have been detected even at lower doses, and the LOAELs for significantly increased tumour incidences will be well below 3 mg/kg body weight per day in rats and 6 mg/kg body weight per day in mice.

1,2,3-Trichloropropane is carcinogenic in rats and mice, inducing a wide range of tumours in both sexes. Data on mode of action, including studies on metabolism, genotoxicity, and determination of DNA adduct formation, suggest that the mechanism of induction of tumours involves direct interaction of an active metabolite with genetic material. Hence, exposure to 1,2,3-trichloropropane should be avoided.

The acute toxicity of 1,2,3-trichloropropane was tested using a variety of aquatic species from different trophic levels.

A sample risk characterization according to the European Commission with respect to the aquatic environment was performed by calculating the ratio between a local predicted environmental concentration (PEC), based on measured data, and a corresponding predicted no-effect concentration (PNEC).

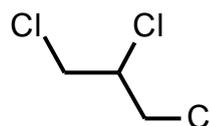
A PNEC for surface water was estimated from the lowest EC₅₀ value from tests carried out in closed systems to minimize 1,2,3-trichloropropane losses. The 48-h EC₅₀ value for *Daphnia magna* immobilization (20 mg/litre) was used to derive the PNEC, together with an uncertainty factor of 1000: PNEC = 20 mg/litre ÷ 1000 = 0.02 mg/litre. Although a lower value was obtained for *Ceriodaphnia cf. dubia* (48-h EC₅₀ of 4.1 mg/litre), this test was based on nominal concentrations only and therefore was not used in the risk characterization.

Using the highest recently measured concentration of 1,2,3-trichloropropane in surface water (2.2 µg/litre) as the PEC, the hazard quotient (PEC/PNEC) becomes 2.2 µg/litre ÷ 0.02 µg/litre = 110. Because this is less than 1, no further information, testing, or risk reduction measures are required.

No data were identified on the toxic effects of this chemical on terrestrial invertebrates or higher plants. For the terrestrial compartment, the available toxicity studies measuring the inhibition of soil-bound microbial activity by 1,2,3-trichloropropane cannot be regarded as sufficient to support a quantitative risk characterization.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

1,2,3-Trichloropropane (CAS No. 96-18-4; C₃H₅Cl₃) is also known as allyl trichloride, trichlorohydrin, and glycerol trichlorohydrin. At room temperature, 1,2,3-trichloropropane is a clear, colourless, moderately flammable liquid with a distinct odour. The environmentally relevant physicochemical properties of 1,2,3-trichloropropane are summarized in Table 1. Additional physical and chemical properties are presented in the International Chemical Safety Card reproduced in this document.



1,2,3-trichloropropane

The purity of the commercially available compound is >98–99.9%. Impurities greater than 0.1% have been identified as isomers of chlorohexane and chlorohexadiene, and there are several unidentifiable impurities (each <0.1%) (NTP, 1993).

Table 1: Physicochemical properties of 1,2,3-trichloropropane.

Property	Value	Reference
Relative molecular mass	147.43	
Density (g/cm ³)	1.38 (20 °C)	Rassaerts & Witzel (1975)
Melting point (°C)	-14.7	Lide (1995)
Boiling point (°C)	156	Miermans et al. (2000)
Vapour pressure (kPa)	0.492 (25 °C)	Lide (1995)
Air saturation (g/m ³)	16 (20 °C)	Verschueren (1996)
<i>n</i> -Octanol/water partition coefficient	2.54 (calculated)	Ruelle (2000)
(log <i>K</i> _{ow})	2.27 (measured)	MITI (1992)
Water solubility (g/litre)	1.75 (25 °C)	Albanese et al. (1987)
Henry's law constant		
Pa·m ³ /mol	31.82 (25 °C, calculated)	Dilling (1977)
dimensionless	0.013	
Pa·m ³ /mol	22.83 (25 °C, measured)	Tancredi & Yanagisawa (1990)
dimensionless	0.009	

Conversion factors¹ for 1,2,3-trichloropropane in air at 20 °C and 101.3 kPa are as follows:

$$1 \text{ mg/m}^3 = 0.16 \text{ ppm}$$

$$1 \text{ ppm} = 6.1 \text{ mg/m}^3$$

¹ In keeping with WHO policy, which is to provide measurements in SI units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

3. ANALYTICAL METHODS

Selected methods for the detection and quantification of 1,2,3-trichloropropane in different matrices are given here. Additional and more detailed information is available in BUA (1993), IARC (1995), and references cited therein.

Analysis of 1,2,3-trichloropropane in air usually involves sorption of the chlorinated alkane onto a solid matrix, followed by thermal or solvent desorption prior to gas chromatography/flame ionization detection (GC/FID), gas chromatography/photoionization detection/electrolytic conductivity detection (GC/PID/ELCD), or gas chromatography/mass spectrometry (GC/MS). Yamamoto et al. (1998), using GC with ELCD, reported a detection limit of about 2 mg/m³. Peng & Batterman (2000) as well as Bonvalot et al. (2000), employing GC/MS, reported a method detection limit of 0.04 µg/m³. Pankow et al. (1998), also using GC/MS, reported a detection limit of about 30 µg/m³. Both Brock & Carroll (1985) and Bouhamra et al. (1997) analysed air samples by similar techniques, but without specifying detection limits.

For water, purge and trap techniques followed by gas chromatography/electron capture detection (GC/ECD) or GC/MS are generally employed. Bauer (1981a) reported a detection limit of 0.07 µg/litre, Zearth et al. (1998) determined a limit of quantification of 0.1 µg/litre, and Miermans et al. (2000) obtained a limit of detection of 0.0004 µg/litre. Yoshikawa et al. (1998) employed a similar system, although detection limits were not specified.

Sediment was analysed by GC/ECD after nitrogen blow-out, adsorption, and solvent elution, with a detection limit of 1 µg/kg (LWA, 1989). For the detection of 1,2,3-trichloropropane in sediments, Kawata et al. (1997) used GC/MS for head space analysis after thermal equilibration, obtaining a detection limit of 1 ng/g, while Zearth et al. (1998) employed head space GC/ELCD, with a limit of detection of 0.2 µg/kg.

Bauer (1981a) determined the presence of 1,2,3-trichloropropane in human tissue samples after blow-out and sorption techniques by GC/ECD, with a detection limit of 13 µg/kg.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

According to BUA (1993), there are no known natural sources of 1,2,3-trichloropropane.

Not only is 1,2,3-trichloropropane manufactured itself, but it is also produced in significant quantities as a by-product of the production of other chlorinated compounds, including epichlorohydrin (NTP, 2000).

Moorman et al. (2000) cited an annual production of 9000–14 000 tonnes of 1,2,3-trichloropropane for the USA. Less than about 50 000 tonnes of 1,2,3-trichloropropane is produced annually, globally, as a by-product of epichlorohydrin production. There are about 20–30 epichlorohydrin-producing facilities in North America, Europe, and Asia (The Society of the Plastics Industry [SPI] Epichlorohydrin Task Group, personal communication, 2002).

1,2,3-Trichloropropane is used as an intermediate in the synthesis of other chemicals (e.g., pesticides) in closed systems and as a crosslinking agent in the production of polymers, such as polysulfides and hexafluoropropylene (SPI Epichlorohydrin Task Group, personal communication, 2002). Older reports identified 1,2,3-trichloropropane as a solvent for hydrophobic compounds and resins, as a paint and varnish remover, and as a degreasing agent (Johnson, 1968; Ellerstein & Bertozzi, 1982; Lewis, 1992; BUA, 1993; IARC, 1995; and references cited therein), but it is probably not marketed in consumer products today. The majority (>80%) of the 1,2,3-trichloropropane produced as a by-product of epichlorohydrin production is incinerated on-site (SPI Epichlorohydrin Task Group, personal communication, 2002).

According to data from the US EPA (1999), in 1999, about 11.9 tonnes of 1,2,3-trichloropropane were released into the environment both on-site and off-site, about 5.74 tonnes entered the atmosphere, 0.92 tonnes were discharged into surface water, and about 3.37 tonnes were released into the geosphere.

In general, 1,2,3-trichloropropane may be released during its manufacture, during the manufacture of other industrial chemicals (e.g., epichlorohydrin), which forms 1,2,3-trichloropropane as an unwanted by-product, or by its application or the application of products containing 1,2,3-trichloropropane as an impurity. For example, the presence of 1,2,3-trichloropropane in pesticides and nematocides employed in soil fumigation (Telone, for example, reportedly contains up to 0.17% 1,2,3-trichloropropane by weight; Zearth et al., 1998) has been identified as a potential source for the release of this

chlorinated compound into the environment (Zebarth et al., 1998; City of Shafter, 2000). In addition, 1,2,3-trichloropropane can be present in formulations employed as a well drilling aid and, as such, can lead to contamination of drinking-water (Health Canada, 2000).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 Environmental transport and distribution

The predominant target compartment for 1,2,3-trichloropropane in the environment is air (about 85%), followed by water (about 11%; Level I calculation, six-compartment model; Mackay et al., 1993). Due to its experimentally determined water solubility of 1.75 g/litre, a significant proportion of this compound should be removed from the atmosphere by washout. According to Thomas (1990), the measured Henry's law constant of $22.83 \text{ Pa}\cdot\text{m}^3/\text{mol}$ (Tancrede & Yanagisawa, 1990) indicates moderate volatility from the aqueous phase. In fact, Dilling (1977) determined a half-life of 56 min for the stripping of 1,2,3-trichloropropane from water, while Albanese et al. (1987) found half-lives of 92 min (fresh water) and 93 min (seawater). Tancrede et al. (1992), when employing 1,2,3-trichloropropane-spiked tap water, found an evaporation of =83% at flow rates from 9.7 to 13.6 ml/min and at three different temperatures (25, 33, and 42 °C).

Using sandy and silty loam, Anderson et al. (1991) showed the abiotic loss of 1,2,3-trichloropropane from soil, with half-lives of 2.2–3.5 days. Although this depletion was probably due to evaporation, 1,2,3-trichloropropane will, under environmental conditions, be prone to washout from soil, as its K_{oc} values in the range of 77–95 (measured using a silty and a sandy loam; Walton et al., 1992) indicate a high mobility in soil (Swann et al., 1983; Blume, 1990). Experimental results showing the appearance of 1,2,3-trichloropropane in groundwater (Baier et al., 1987; Oki & Giambelluca, 1989) after the application of nematicides containing 1,2,3-trichloropropane prove the potential of this non-polar chlorinated alkane to contaminate groundwater.

The measured bioconcentration factors (determined according to OECD guideline 305C) in the range of 3–13 (MITI, 1992) indicate no significant bioaccumulation potential for 1,2,3-trichloropropane.

5.2 Abiotic transformation

Using the calculated hydroxyl radical reaction rate constant (K_{OH}) of Atkinson (1987) and assuming a

hydroxyl radical concentration of 5×10^5 molecules/cm³, a half-life of 27.2 days was calculated for 1,2,3-trichloropropane in the atmosphere (BUA, 1993). When applying the US Environmental Protection Agency (EPA) modelling program AOPWIN (Version 1.9), a half-life of about 30.5 days can be calculated, using a rate constant for the hydrogen abstraction (K_{OH}) of $0.3511 \times 10^{-12} \text{ cm}^3/\text{s}$ per molecule and a hydroxyl radical concentration of 1.5×10^6 molecules/cm³. Hence, 1,2,3-trichloropropane released into the atmosphere might undergo a very slow degradation in this environmental compartment in the presence of a sufficient concentration of photochemically produced hydroxyl radicals. Hydrolysis of 1,2,3-trichloropropane seems to be of minor importance, with calculated half-lives of 44 and 74 years (Ellington et al., 1987; Milano et al., 1988).

5.3 Biotransformation and biodegradation

In aerobic biodegradation tests performed according to OECD guideline 301C, 1,2,3-trichloropropane was not readily biodegradable (biological oxygen demand 0% of theoretical oxygen demand, incubation for 28 days; MITI, 1992). In a preliminary study (Vannelli et al., 1990), the co-oxidative transformation of 1,2,3-trichloropropane by the ammonia-oxidizing bacterium *Nitrosomonas europaea* was shown. In the experiments described, the chlorinated substrate (at a concentration of about 6.8 µmol/litre) was reduced to a residual amount of 91% (in the absence of the energy source ammonia) and to 77% (in the presence of ammonia) after 24 h of incubation. More recent studies employing the methanotroph *Methylosinus trichosporium* demonstrated that the recalcitrant 1,2,3-trichloropropane is co-metabolically converted to a range of different products, such as chlorinated propanols (Bosma & Janssen, 1998). To date, all attempts to isolate cultures able to utilize 1,2,3-trichloropropane as a sole source of carbon and energy have failed. Even though a modified strain of *Agrobacterium radiobacter* (expressing an efficient haloalkane dehalogenase from a *Rhodococcus* sp.) did utilize the analogous 1,2,3-tribromopropane for growth, 1,2,3-trichloropropane was not used and only slowly converted (Bosma et al., 1999). Peijnenburg et al. (1998) observed the reductive transformation of 1,2,3-trichloropropane by using anaerobic sediments and determined that reductive dehalogenation was the sole reaction to take place. They calculated a zero-order reaction constant of 0.71 mmol/litre per day. Hauck & Hegemann (2000) described an anaerobic bioreactor system inoculated from river sediment, which converted 1,2,3-trichloropropane. However, neither analytical nor kinetic data were presented for 1,2,3-trichloropropane. Nevertheless, although results reported by Anderson et al. (1991) indicated a lack of biodegradation of 1,2,3-trichloropropane in clay loam, reductive dehalogenation of this compound might take place in anaerobic sediments.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 Atmosphere

In Bochum, Germany, concentrations of 1,2,3-trichloropropane not exceeding $0.4 \mu\text{g}/\text{m}^3$ were detected (Bauer, 1981b). Bonvalot et al. (2000) reported the presence of 1,2,3-trichloropropane in ambient air sampled at the Rivière des Prairies, Montreal, Canada, station at levels of up to $0.21 \mu\text{g}/\text{m}^3$. Pankow et al. (1998) were not able to detect 1,2,3-trichloropropane in New Jersey, USA, air using sampling sites ranging from a low to high degree of urbanization and traffic. Similarly, while Yamamoto et al. (1998) did not detect 1,2,3-trichloropropane in the urban air of Yokohama, Japan, Peng & Batterman (2000) failed to detect 1,2,3-trichloropropane in ambient air sampled along roads at “rush hour” periods in Detroit, USA. However, Bouhamra et al. (1997) reported a mean value of $491 \mu\text{g}$ 1,2,3-trichloropropane/ m^3 in ambient air sampled at 19 different locations in Kuwait.

Peng & Batterman (2000) failed to detect 1,2,3-trichloropropane in air from an office building sampled in an indoor air quality study in Ann Arbor, USA. Bouhamra et al. (1997) found a maximum concentration of $34.3 \text{ mg}/\text{m}^3$ in indoor air sampled in residences in Kuwait. However, they were not able to correlate this to a specific source. Using their data, they calculated an average indoor/outdoor concentration ratio for 1,2,3-trichloropropane of 5.06 for Kuwait. There is no obvious reason for these exceptionally high values for ambient and indoor air in Kuwait, and the reports have yet to be substantiated.

6.1.2 Hydrosphere

The presence of 1,2,3-trichloropropane in European rivers has been frequently reported. In a river monitoring program, 1,2,3-trichloropropane was detected in Dutch surface water of the rivers Rhein, Meuse, and Westerscheldt and the Northern Delta Area, with the highest concentration up to $2.2 \mu\text{g}/\text{litre}$ (Miermans et al., 2000). Liska et al. (1996) identified 1,2,3-trichloropropane at five sampling points along the river Nitra, Slovakia, in a European river monitoring program, although no concentrations were given. In a follow-up study by Frischenschlager et al. (1997), 1,2,3-trichloropropane was detected at a concentration of $1.6 \mu\text{g}/\text{litre}$ at one sampling site. An extensive compilation of monitoring data summarizing the appearance of 1,2,3-trichloropropane in selected rivers, such as Rhein, Emscher, Elbe, and Weser, with sampling sites in Germany and the

Netherlands, showed maximum concentrations not exceeding $0.6 \mu\text{g}/\text{litre}$ in the years 1981–1989 (BUA, 1993, and references cited therein). Yamamoto et al. (1997) detected 1,2,3-trichloropropane in 18 of 28 samples of water from rivers and estuaries in Osaka City, Japan; concentrations ranged from 0.18 (detection limit) to about $100 \mu\text{g}/\text{litre}$. The authors found that 1,2,3-trichloropropane was not completely eliminated by the sewage treatment process, with a maximum concentration of approximately $90 \mu\text{g}/\text{litre}$ found in effluent discharges. Yoshikawa et al. (1998) detected 1,2,3-trichloropropane in seawater sampled near Kawasaki City, Japan, but concentrations were not given.

Groundwater samples from the Netherlands and the USA were shown to contain 1,2,3-trichloropropane due to the application of impure nematicides. Accordingly, Lagas et al. (1989) reported 1,2,3-trichloropropane concentrations of up to $5.6 \mu\text{g}/\text{litre}$ in groundwater samples from two potato plantations in the Netherlands. In the USA, both Oki & Giambelluca (1989) and Baier et al. (1987) reported 1,2,3-trichloropropane in groundwater, with maximum concentrations of about $2 \mu\text{g}/\text{litre}$ (Hawaii) and $>100 \mu\text{g}/\text{litre}$ (New York State). More recently, Zearth et al. (1998) reported a maximum value of $0.86 \mu\text{g}/\text{litre}$ in water sampled from a contaminated aquifer in British Columbia, Canada, with levels up to $0.92 \mu\text{g}/\text{kg}$ in the corresponding sediment.

Drinking-water sampled from 100 German cities did not exceed a maximum concentration of $0.1 \mu\text{g}$ 1,2,3-trichloropropane/litre (Bauer, 1981b). Gelover et al. (2000) detected 1,2,3-trichloropropane in drinking-water supplies in Mexico but failed to quantify the amounts present. However, more recently, 1,2,3-trichloropropane was detected in drinking-water in the USA (Puhi, Kaua’i, Hawaii; and City of Shafter, California) at concentrations of $0.1 \mu\text{g}/\text{litre}$ (Kaua’i Department of Water, 2001) and up to $0.24 \mu\text{g}/\text{litre}$ (City of Shafter, 2000).

6.2 Human exposure

6.2.1 General population exposure

The most likely routes of exposure of the general population to 1,2,3-trichloropropane are via air and water. This is due to the fact that 1,2,3-trichloropropane will preferably partition into air and water (Mackay et al., 1993). Human exposure will therefore occur by inhalation of contaminated air or by ingestion of 1,2,3-trichloropropane-containing water. In view of this, it is important to consider that indoor air is more likely to contain higher concentrations of 1,2,3-trichloropropane than outdoor air, due to the greater number of potential sources and lower rates of ventilation (Bouhamra et al., 1997). 1,2,3-Trichloropropane might be taken up as well via food, as von Düselen et al. (1982) estimated (using

the 1976 German Nutrition Report consumption patterns) an average daily intake of 7.4 µg per person, but gave no further details.

Assuming a daily intake of 7.4 µg per person via food, a daily consumption of 2 litres of drinking-water containing 0.1 µg 1,2,3-trichloropropane/litre, a daily intake of 20 m³ air with an average 1,2,3-trichloropropane concentration of 0.1 µg/m³, and a body weight of 64 kg, an estimated daily intake of 150 ng/kg body weight can be calculated. Omitting the amount of 1,2,3-trichloropropane taken up via food lowers the daily intake to about 34 ng/kg body weight. Using the above assumptions but the reported much higher values for air in Kuwait (outdoor air 491 µg/m³, indoor air 2480 µg/m³ [i.e., 5.06 × 491]) and assuming that 50% of the time is spent outdoors and 50% indoors, one can calculate a daily intake of about 464 µg/kg body weight. Omitting the amount of 1,2,3-trichloropropane taken up via food has no effect on this daily intake.

6.2.2 Occupational exposure

Occupational exposure is by inhalation and dermal exposure through the industrial production and use of 1,2,3-trichloropropane. However, there is a lack of information on dermal exposure and intake.

The only data available on inhalation exposure are those relating to 1,2,3-trichloropropane-containing air (Brock & Carroll, 1985). Brock & Carroll (1985) reported a maximum short-term exposure concentration of 17 mg 1,2,3-trichloropropane/m³ for maintenance personnel at a chemical plant in the USA. However, exposure concentrations in other workplaces did not usually exceed 0.61 mg/m³. These workplace concentrations (workday situation: daily consumption of 20 m³ air, accrued 1-h peak concentration with 17 mg/m³, 7-h on-site ambient air with <0.61 mg/m³, remaining time ambient air with 0.1 µg/m³; intake via food and drinking-water not accounted for) might lead to a daily intake of up to 277 µg/kg body weight.

6.2.3 Levels in humans

Only one report is available on 1,2,3-trichloropropane detected in human tissues. Random human pathology samples (i.e., from lung, liver, muscle, kidney from 3 females and 12 males, age 31–78) were analysed; only in adipose tissue of the fibrous capsule of the kidney was 1,2,3-trichloropropane found, at an average concentration of 3.1 µg/kg fresh weight (with a stated maximum value of 15.1 µg/kg) (Bauer, 1981b).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 Absorption, distribution, and excretion

Following a single administration of [¹⁴C]1,2,3-trichloropropane in corn oil by gavage to male and female F344 rats (30 mg/kg body weight) and male B6C3F1 mice (30 and 60 mg/kg body weight), 1,2,3-trichloropropane was rapidly absorbed, metabolized, and excreted. The major route of excretion was in the urine. By 60 h post-dosing, rats had excreted 50% and mice 65% by this route. Excretion in the faeces and exhalation as ¹⁴CO₂ each accounted for 20% of the total dose in 60 h in rats and for 15 and 20%, respectively, in mice. At 60 h, in both rats and male mice, ¹⁴C activity was mainly concentrated in liver, kidney, and forestomach, the majority of the tissue ¹⁴C activity being not extractable and apparently covalently bound to protein. In rats, no apparent sex-related differences were observed in the ability to excrete 1,2,3-trichloropropane-derived radioactivity. Male mice eliminated 1,2,3-trichloropropane-derived radioactivity more rapidly than rats, and lower concentrations of radioactivity were found in tissues 60 h after dosing in mice (Mahmood et al., 1991).

Pharmacokinetic studies in male F344/N rats after intravenous administration of 3.6 mg 1,2,3-trichloropropane/kg body weight showed that 1,2,3-trichloropropane is rapidly distributed and eliminated (Volp et al., 1984), with higher elimination from blood than from tissue. This conclusion is based on the observation that the radiolabel had longer half-lives than 1,2,3-trichloropropane in muscle, skin, adipose tissue, liver, and kidney. The biphasic elimination kinetics are characterized by values of *t*_{1/2}(1) of 0.3–1.8 h and *t*_{1/2}(2) of 30–45 h for 1,2,3-trichloropropane and values of *t*_{1/2}(1) of 2.1–5.3 h and *t*_{1/2}(2) of 87–182 h for the radiolabel (Volp et al., 1984). In bile, 30% of the dose appeared within 6 h, presumably as GSH conjugates. As faecal excretion accounted for only 18% of the dose, a significant amount of the dose seemed to be reabsorbed from the intestines. The highest tissue ¹⁴C concentrations were found in adipose tissue, liver, and kidney after 1, 4, and 24 h, respectively.

Results of acute toxicity studies (see section 8.1) show that 1,2,3-trichloropropane can be dermally absorbed, although to a more limited extent than via the gastrointestinal tract.

7.2 Biotransformation

Evidence suggests that 1,2,3-trichloropropane can be metabolized by two major pathways in rats and mice

(see Figure 1). One proposed pathway in the liver involves mixed-function oxidase-catalysed oxygenation of 1,2,3-trichloropropane on a terminal carbon to yield a chlorohydrin, followed by additional reactions that result in the formation of the observed metabolites.

A second pathway in the liver involves GSH transferase-catalysed formation of GSH conjugates, which either undergo additional biotransformation in the liver or are excreted in bile or plasma. However, neither these metabolic pathways nor the metabolites are well characterized.

In rats, the major urinary metabolite (40% of urinary radioactivity) identified after 6 h is a mercapturic acid conjugate, *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine, or ACPC. In the 24-h urine, a second metabolite, a cysteine conjugate (*S*-(3-chloro-2-hydroxypropyl)-L-cysteine), or CPC, was determined. After intravenous injection of 1,2,3-trichloropropane to rats, one of the three major metabolites in the bile was (2-(*S*-glutathionyl)malonic acid), or GMA (Mahmood et al., 1991). The metabolic profile in female rats was similar to that in males, but the metabolites were present at lower levels. In male mice, the urinary metabolite spectrum is more complex, and ACPC was only a minor component (only 3% of urinary radioactivity). Several unidentified metabolites are excreted in higher amounts. Female mice were not studied.

In vitro studies showed the NADPH-dependent formation of 1,3-dichloroacetone (DCA, a direct-acting mutagen; Merrick et al., 1987) from 1,2,3-trichloropropane in the presence of human and rat microsomes. DCA was formed at a rate of 0.27 nmol/min per milligram protein with microsomes from rat liver and at a rate of 0.03 nmol/min per milligram protein with microsomes from a human liver sample. An increase in the rate of DCA formation was observable after phenobarbital- and dexamethasone-mediated induction of cytochrome P-450. In the presence of alcohol dehydrogenase and NADH, 1,3-dichloro-2-propanol and 2,3-dichloropropanol were detected as secondary metabolites of DCA and 2,3-dichloropropanal (Weber & Sipes, 1992).

7.3 Covalent binding

Covalent binding to hepatic macromolecules was investigated after intraperitoneal administration of 30 mg 1,2,3-trichloropropane/kg body weight to rats. Four hours post-administration, the extent of covalent binding to protein, RNA, and DNA was 418, 432, and 244 pmol 1,2,3-trichloropropane equivalents/mg, respectively. Whereas binding to protein reached a maximum at 4 h and then decreased significantly to the next measured time point (at 24 h post-administration), the maximum

DNA binding was reached at 24 h post-administration. The binding to both hepatic protein and DNA was cumulative for up to three dosages given 24 h apart. GSH may play a dual role in covalent binding: supporting the binding of 1,2,3-trichloropropane to hepatic DNA and inhibiting the binding to protein. It was assumed that several metabolic pathways take part in the activation and covalent binding of 1,2,3-trichloropropane (Weber & Sipes, 1990).

Significant DNA adduct levels were measured in several target and non-target tissues of tumorigenesis after single gavage dosages of 3 and 30 mg/kg body weight in male Fischer 344 rats and 6 and 60 mg/kg body weight in male B6C3F1 mice (see section 8.4.2).

In the DNA of rat liver after intraperitoneal administration of 300 mg 1,2,3-trichloropropane/kg body weight, one major adduct, *S*-[1-(hydroxymethyl)-2-(*N*⁷-guanyl)ethyl]glutathione, was identified (La et al., 1995), confirming the role of GSH in adduct formation. Pretreatment of rats with phenobarbital (induction of cytochrome P-450) as well as GSH depletion caused a decrease in covalent DNA binding (Weber & Sipes, 1990, 1992). *S*-[1-(hydroxymethyl)-2-(*N*⁷-guanyl)ethyl]glutathione was formed in forestomach, liver, glandular stomach, and kidney after repeated dosing either by gavage or by drinking-water (see section 8.4.2) (La et al., 1996).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

1,2,3-Trichloropropane is of moderate acute toxicity.

A 4-h LC₅₀ of about 3000 mg 1,2,3-trichloropropane/m³ was determined for rats and mice from a compilation of mortality rates after single inhalation exposure to high concentrations for 0.5–4 h. Symptoms of intoxication included prostration, hypoactivity, ataxia, sedation, dyspnoea, convulsions, lacrimation, salivation, irritation of the mucosa of eyes and nose, and liver and kidney damage. Immediate respiratory depression was a frequent cause of death. Delayed deaths (after 7–10 days) were ascribed to liver damage (MAK, 1993). Significant increases in the serum enzymes glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and ornithine carbamyl transferase up to 48 h after a single 4-h inhalation exposure to 3100 mg 1,2,3-trichloropropane were indicative of hepatic damage in rats (Drew et al., 1978).

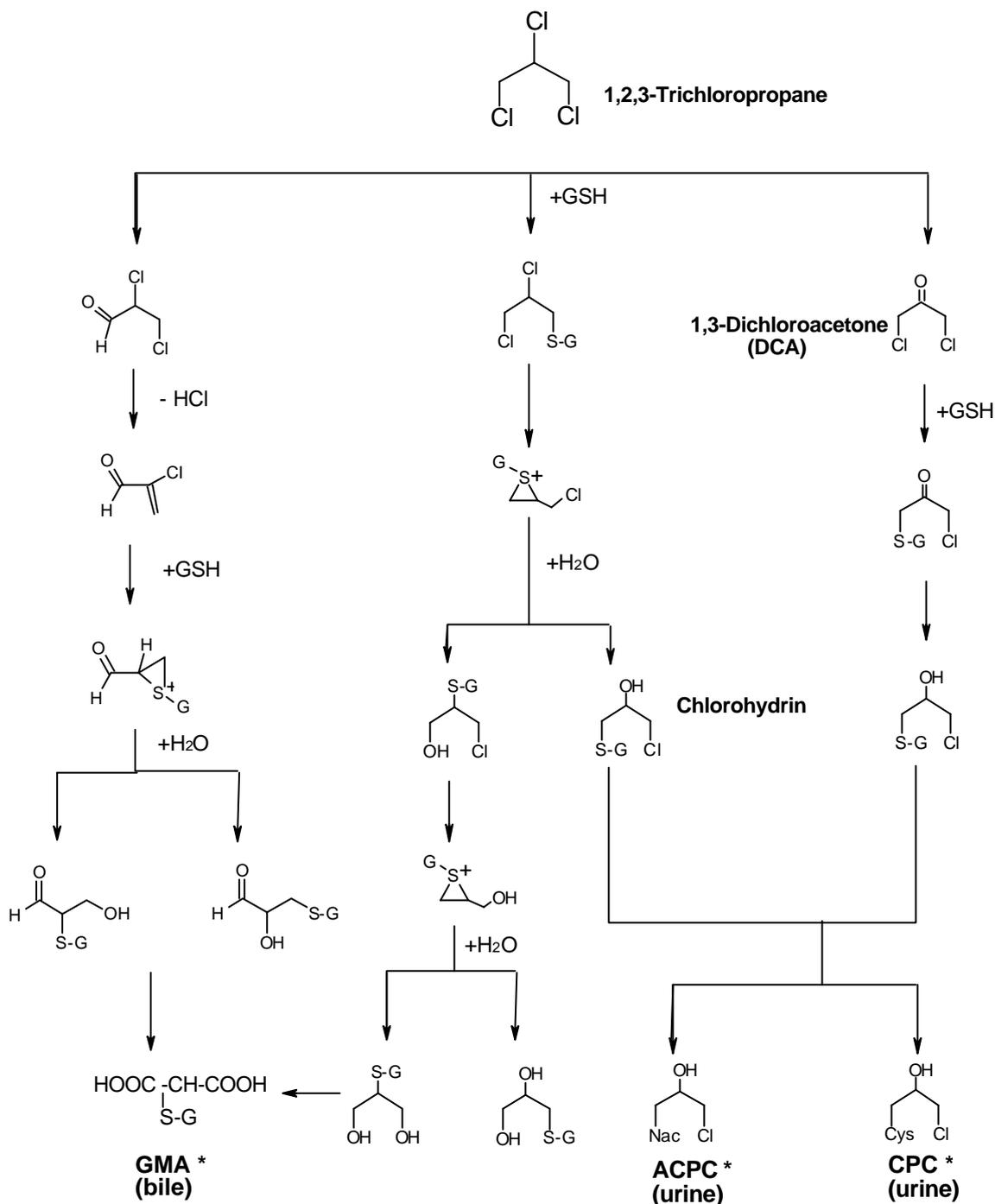


Fig. 1: Possible metabolic pathways in rats (Mahmood et al., 1991)

[ACPC = N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC = S-(3-chloro-2-hydroxypropyl)-L-cysteine; GMA = 2-(S-glutathionyl)malonic acid]

Oral LD₅₀ values in the rat range from 150 to 500 mg/kg body weight (MAK, 1993).

Dermal toxicity is lower, with reported LD₅₀ values of 836 mg/kg body weight in rats and 384–2457 mg/kg body weight in rabbits (MAK, 1993).

In comparison with other tested chloro-, bromo-, and mixed chlorobromopropanes, 1,2,3-trichloropropane showed a very low potency as a nephrotoxicant after a single intraperitoneal application of 1, 2, or 3 mmol/kg body weight (147, 294, or 441 mg/kg body weight). 1,2,3-Tribromopropane was the most potent. In the mid- and high-dose groups exposed to 1,2,3-trichloropropane, 1/5 and 3/5 male Wistar rats died, respectively. Forty-eight hours after application, relative kidney weight and urea excretion were dose-dependently increased (no comment on significance), and histopathological examination detected moderate kidney necrosis in one of the two surviving animals of the high-dose group. Significant DNA damage (DNA single strand breaks determined by alkaline elution) was reported starting from dosages of 0.375 mmol/kg body weight (Låg et al., 1991).

8.2 Irritation and sensitization

A dose of 0.5 ml of 1,2,3-trichloropropane applied to the intact skin of rabbits (5 males, 1 female) for 4 h under semi-occlusive and for 24 h under occlusive dressings produced mild reversible irritation, with a primary irritation index of 2.5 for the 24-h application (maximum possible value 8.0) (Bio/dynamics Inc., 1985a). Comparable results were reported for intact (12 rabbits, sex not given) and abraded skin of rabbits (3 males, 3 females), with a primary irritation index of 1.63 (maximum possible value 8.0) (Albert, 1982). In contrast to these test results, another study classified 1,2,3-trichloropropane as severely irritating, based on irritation scores from a Draize test (0.5 ml 1,2,3-trichloropropane, 24-h occlusive application) on intact and abraded skin of rabbits (3 males, 11 females). The mean scores were from 1.6 to 3.0 on a standard scale ranging from 0 to 4 (Clark, 1977). Therefore, direct contact of 1,2,3-trichloropropane with the skin causes slight irritation or strong irritation if confined to the skin.

After instillation of 0.1 ml of undiluted 1,2,3-trichloropropane, mild to moderate irritation of rabbit eyes was observed (conjunctival irritation, conjunctival necrosis, clouding of the cornea, iris damage), with all effects being reversible within 2–7 days (Bio/dynamics Inc., 1985b). Another eye irritation test (Draize test) reported less severe effects, leading to a classification of 1,2,3-trichloropropane as mildly irritating to rabbit eyes after 1–2 h (Clark, 1977). With a maximal irritation score of 20.0 out of a possible 110.0 at 6 h after

instillation, undiluted 1,2,3-trichloropropane was classified as moderately irritating to the eye (Albert, 1982).

In the guinea-pig maximization test (Magnusson and Kligman test), only a very mild sensitizing activity of 1,2,3-trichloropropane was found (2/20 guinea-pigs with a positive reaction, 1/20 with a weak reaction; effects entirely reversible within 48 h). The applied concentrations of 1,2,3-trichloropropane were a 0.1% solution in corn oil for intradermal induction, 50% in corn oil for topical induction, and 25% for topical challenge. Results were scored on removal of the challenge patch and 24 and 48 h later (Clark, 1977; MAK, 1993).

A lack of sensitizing effects of 1,2,3-trichloropropane was reported in groups of five male and five female Dunkin-Hartley guinea-pigs. Induction was by weekly topical treatment with 0.5 ml undiluted 1,2,3-trichloropropane under occlusive bandages for 6 h over a 3-week period, followed by one challenge application after a 2-week rest period. Further groups were treated with corn oil as negative control and 2,4-dinitrochlorobenzene as positive control. Results were scored on removal of the challenge patch and 24 and 48 h later. One male and one female exposed to 1,2,3-trichloropropane were found dead on day 3 and day 11, respectively (Albert, 1982). The absence of any dermal response to undiluted 1,2,3-trichloropropane was also observed in Hartley albino guinea-pigs in a sensitization study conducted according to the Buehler method (induction: nine 6-h occlusive applications in 3 weeks followed by challenge after 2 weeks, readings after 24 and 48 h) (Bio/dynamics Inc., 1985c).

8.3 Short- and medium-term exposure

8.3.1 Inhalation

F344 rats and B6C3F1 mice were exposed to concentrations of 0, 80, 240, or 780 mg 1,2,3-trichloropropane/m³, 6 h/day, for a total of 9 days during an 11-day interval (Miller et al., 1986a). A significant decrease in body weight was noted only in rats, at all doses, while the body weights of mice were unaffected, even though both species had decreased abdominal fat at all doses. Reduced food consumption was observed at the highest concentration only. There was a significant increase in absolute and relative liver weights in the 780 mg/m³ groups of rats and mice. There were no microscopic changes in the liver indicative of severe hepatotoxicity, nor were there any changes in serum enzymes that were diagnostic of liver injury. There were no gross or histopathological changes in kidneys of either rats or mice. In mice, testes weights were significantly reduced at 780 mg/m³, but without associated histopathological changes (Miller et al., 1986a).

The primary effect of exposure to 1,2,3-trichloropropane in rats and mice in the same study was a microscopic degenerative and inflammatory change in the nasal olfactory mucosa (Miller et al., 1986a). Besides nasal exudate at the lowest dose in both species, degeneration of the epithelium was observed in rats at 80 mg/m³ and in mice at 240 mg/m³. Further nasal exostosis and fibrotic changes were detectable in rats at 780 mg/m³, whereas mice showed nasal exostosis from 240 mg/m³. Concentration-dependent adverse effects on nose tissue were more severe in rats than in mice.

Follow-up studies in F344 rats and B6C3F1 mice using lower concentrations of 1,2,3-trichloropropane (6, 18, and 61 mg/m³) for the same period were performed to derive NOAELs for the most sensitive end-point, changes in the olfactory epithelium detectable by histopathological examination of nose tissue (Miller et al., 1986b). The LOAEL for decreased thickness and inflammatory changes of the olfactory epithelium was 18 mg/m³ for rats and 61 mg/m³ for mice; the NOAEL was 6 mg/m³ for rats and 18 mg/m³ for mice. Neither signs of intoxication nor systemic effects were reported at any of these concentrations (Miller et al., 1986b).

Groups of CD rats (15 males and 15 females per group) were exposed by inhalation to 1,2,3-trichloropropane (purity 98.9%) for 13 weeks (6 h/day, 5 days/week) at concentrations of 0, 28, 92, and 300 mg/m³. Body weight decreases were noted in mid- and high-dose females only. Increases in liver weights were observed in males in all dose groups and in females in the mid- and high-dose groups. Signs of distinct respiratory tract irritation (i.e., red nasal discharge and excessive lacrimation) were reported at 92 mg/m³ and higher. Hepatocellular hypertrophy was observed in male rats at all doses. Dose-related focal peribronchial lymphoid hyperplasia was found primarily in males, whereas splenic extramedullary haematopoiesis was observed only in females at all 1,2,3-trichloropropane concentrations (Bio/dynamics Inc., 1979; Johannsen et al., 1988).

A follow-up 13-week study with lower 1,2,3-trichloropropane concentrations (0, 3.1, and 9.2 mg/m³) reported signs of irritation of mucous membranes (increase of lacrimal discharge), even at the lowest concentration of 3.1 mg/m³. However, histopathological examination of the nasal epithelium showed no treatment-related effects at any concentration. The only systemic effects were changes of haematological parameters and increases in lung and ovary weights without corresponding microscopic findings (Bio/dynamics Inc., 1983; Johannsen et al., 1988).

8.3.2 Oral exposure

1,2,3-Trichloropropane (99% in 0.5% Emulphor; 1, 10, 100, and 1000 mg/litre) was administered for 13 weeks via drinking-water to male and female Sprague-Dawley rats (10 males and 10 females per group). Significantly decreased water intake was observed by females exposed to 100 and 1000 mg/litre and by males exposed to 1000 mg/litre and subsequently to reduced intake of 1,2,3-trichloropropane. Dosages were specified only for these three dose groups: i.e., 17.6 and 149 mg/kg body weight per day for females (100 and 1000 mg/litre) and 113 mg/kg body weight per day for males (1000 mg/litre). For the highest dosage, body weight gain was significantly reduced in both males and females. The only effects reported for the 100 mg/litre exposure were increased relative liver and kidney weights of females. Weight increases in these organs were found in both sexes for the highest exposure level and were accompanied by minor histological changes in these tissues. Changes of activities of hepatic enzymes (an elevation in serum cholesterol in female rats and induced hepatic aminopyrine demethylase and aniline hydroxylase in male rats) were observed at the highest dose (Villeneuve et al., 1985). The LOAELs for increased relative liver and kidney weights were 17.6 mg/kg body weight per day for female rats and 113 mg/kg body weight per day for male rats when 1,2,3-trichloropropane was administered via drinking-water. The NOAEL is about 2 mg/kg body weight per day (although the authors give the NOAEL as 15–20 mg/kg body weight, in spite of the increased liver weights in females).

F344 rats and B6C3F1 mice were administered 1,2,3-trichloropropane by gavage (>99% purity; in corn oil) at 0, 8, 16, 32, 63, 125, and 250 mg/kg body weight per day, 5 days/week, for up to 17 weeks, with an interim sacrifice at 8 weeks (Hazleton Laboratories America Inc., 1983a, 1983b; NTP, 1993; Irwin et al., 1995). In rats, principal toxic lesions occurred in liver, kidney, and nasal turbinates. After 17 weeks of exposure, absolute liver weight was increased in males of all dose groups and in females from 16 mg/kg body weight per day; kidney weights were increased from 32 mg/kg body weight per day in males and 63 mg/kg body weight per day in females, accompanied by regenerative hyperplasia (observed at interim sacrifice). General toxicity was obvious from decreased body weight of males at 63 mg/kg body weight per day and of both sexes at 125 mg/kg body weight per day. All female rats receiving 250 mg 1,2,3-trichloropropane/kg body weight per day died by week 2, and all males receiving the same dose died by week 5. At 125 mg/kg body weight per day, one male died by the end of week 5, and four females died during the studies. At the two highest dosages (125 and 250 mg/kg body weight per day), histopathology revealed changes indicative of extensive

cellular damage in liver, kidneys, and nasal turbinates. Changes in liver enzymes, pseudocholinesterase, urea nitrogen, creatinine, and bilirubin also pointed to hepatocellular damage. Haematological changes at 16 mg/kg body weight per day and higher dosages were interpreted as non-regenerative anaemia, possibly associated with a depression in erythropoiesis (Hazleton Laboratories America Inc., 1983a). The LOAEL for a 17-week treatment by gavage was 8 mg/kg body weight per day in male rats and 16 mg/kg body weight per day in female rats.

In mice in the same study, main targets of toxic action were lung, liver, and forestomach. Hyperplasia of bronchiolar epithelium and hyperplasia and hyperkeratosis of forestomach were induced by a dosage of 63 mg/kg body weight per day and higher in females. From 125 mg/kg body weight per day, liver weights were significantly increased, accompanied by severe histological changes of the liver at the higher dosage in both sexes. The 250 mg/kg body weight per day dose was distinctly toxic, with increased mortality (16/20 males and 7/20 females) and necrosis of liver and lung tissue (Hazleton Laboratories America Inc., 1983b). Mice tolerated higher doses than rats, with LOAELs of 63 mg/kg body weight per day in female mice and 125 mg/kg body weight per day in male mice.

1,2,3-Trichloropropane in corn oil was administered to male and female Sprague-Dawley rats at doses of 0.01, 0.05, 0.2, and 0.8 mmol/kg body weight per day (1.5, 7.4, 29, and 118 mg/kg body weight per day) for 10 consecutive days and 0.01, 0.05, 0.1, and 0.4 mmol/kg body weight per day (1.5, 7.4, 15, and 59 mg/kg body weight per day) for 90 days (Merrick et al., 1991). Weight gain suppression occurred at a dose of 118 mg/kg body weight per day after 10 days. Liver and kidney weights were increased relative to control in the two highest groups after 10- and 90-day exposures. Serum chemistries and histopathology indicated a mild hepatotoxic response to 1,2,3-trichloropropane in the highest group of each study, but there was no renal toxicity.

In the same study, proliferative or neoplastic lesions in liver, lungs, mammary gland, and forestomach were reported in groups of 10 male and 10 female Sprague-Dawley rats administered 1,2,3-trichloropropane in corn oil by gavage in daily dosages of 0.05 or 0.4 mmol/kg body weight per day (7.4 or 59 mg/kg body weight per day) at the end of the 90-day treatment period (Merrick et al., 1991).

In the same study, myocardial necrosis and degeneration occurred in a diffuse pattern with marked eosinophilia of affected cells. Male and female animals showed a cardiopathic response only at a dose of

118 mg/kg body weight per day after the 10-day exposure. In the 90-day study, the incidence of cardiopathy was higher in males than in females. Adverse effects on myocardium were reported at the lowest dosage of 1.5 mg/kg body weight per day (inflammation: 3/10 males, 1/10 females; necrosis: 2/10 males), but a progression to distinctly higher incidences was observed only for the highest dosage of 58.8 mg/kg body weight per day (inflammation: 8/10 males and females; degeneration: 5/10 males, 8/10 females; necrosis: 6/10 males, 7/10 females) (Merrick et al., 1991).

The cardiotoxic effect could not be confirmed in the National Toxicology Program (NTP) studies with F344/N rats covering a comparable treatment period and in longer-term studies (NTP, 1993). Gavage application in dosages up to 30 mg/kg body weight per day induced no dose-dependent increases in incidence of cardiomyopathy in male rats, and control animals already had high incidences. Likewise, treated B6C3F1 mice in the NTP study did not show any increased cardiotoxicity (NTP, 1993; Irwin et al., 1995).

8.4 Long-term exposure and carcinogenicity

1,2,3-Trichloropropane (>99% purity) in corn oil was administered by gavage to F344/N rats and B6C3F1 mice of both sexes (60 per group) at doses of 3, 10, and 30 mg/kg body weight per day and 6, 20, and 60 mg/kg body weight per day, respectively, for 5 days/week for an intended 104 weeks (NTP, 1993; Irwin et al., 1995; see Tables 2–5). Up to 10 animals per group were scheduled for interim evaluation at 15 months. Because of reduced survival associated with the development of chemical-related neoplasms in rats in the lowest dose groups, rats receiving 30 mg/kg body weight per day were terminated at 65 (females) or 76 weeks (males), and mice receiving 60 mg/kg body weight per day were terminated at 73 (females) or 79 weeks (males); mice receiving 20 mg/kg body weight per day were terminated at 88 weeks (NTP, 1993; Irwin et al., 1995).

Rats showed significantly decreased body weight at 30 mg/kg body weight per day from week 15 in males and from week 53 in females. In male rats, a significant increase in hyperplasia was evident in the forestomach and pancreas at =3 mg/kg body weight per day and in the kidney at =10 mg/kg body weight per day. In female rats, the incidence of hyperplasia in the forestomach and pancreas was statistically significant at =3 mg/kg body weight per day and in the kidney at =30 mg/kg body weight per day. In all dose groups of mice, eosinophilic and basophilic liver foci were noted. Focal hyperplasia of squamous epithelium of the forestomach was significantly increased in male mice of all dose groups, but only in high-dose female mice. Pathological findings

Table 2: Incidence of non-neoplastic lesions and neoplasms after administration of 1,2,3-trichloropropane by gavage to male rats.^a

	Control	3 mg/kg body weight per day	10 mg/kg body weight per day	30 mg/kg body weight per day
Animals surviving to 104 weeks ^b (main study)	34/50	32/50	14/49	0/52
Mean survival (days)	647	661	596	465
	Incidences of lesions and neoplasms (main + interim study)^{c,d,e}			
Oral mucosa	<i>60</i>	<i>60</i>	<i>59</i>	<i>60</i>
Squamous cell papilloma	0	4	10**	22**
Squamous cell carcinoma	1	0	11**	25**
Forestomach	<i>60</i>	<i>60</i>	<i>59</i>	<i>60</i>
Hyperplasia, basal cell	0	7*	12**	9**
Hyperplasia, squamous	3	28**	13*	6
Squamous cell papilloma	0	31**	36**	46**
Squamous cell carcinoma	0	9**	28**	14**
Pancreas	<i>60</i>	<i>60</i>	<i>59</i>	<i>60</i>
Hyperplasia	28	48**	53**	56**
Adenoma	5	21**	37**	31**
Adenocarcinoma	0	0	2	1
Kidney	<i>60</i>	<i>60</i>	<i>59</i>	<i>60</i>
Hyperplasia	0	1	23**	35**
Adenoma	0	2	20**	26**
Preputial gland	<i>59</i>	<i>57</i>	<i>59</i>	<i>58</i>
Adenoma	5	3	6	11*
Carcinoma	0	3	3	6
Adenoma or carcinoma	5	6	9	17**

^a From NTP (1993); Irwin et al. (1995).

^b The reduction in life span of the animals was caused by tumours induced by 1,2,3-trichloropropane.

^c Significantly different (* $P < 0.05$; ** $P < 0.01$) from controls by the life table test (squamous cell carcinoma) or by logistic regression (all other lesions).

^d Number of rats per group necropsied (oral mucosa) or with tissue examined microscopically (forestomach, pancreas, kidney, preputial gland) given in italics.

^e Number of rats with lesion or neoplasm given in bold.

were dominated by preneoplastic and neoplastic lesions (NTP, 1993; Irwin et al., 1995).

Data from the NTP study (NTP, 1993; Irwin et al., 1995) show 1,2,3-trichloropropane to be a multisite carcinogen in both rats and mice, even at the lowest dose. Main targets of tumorigenesis were squamous epithelium cells of forestomach and oral mucosa. Tumour incidences were significantly elevated in oral mucosa in the mid- and high-dose groups of rats, but only in high-dose female mice. Forestomach tumours were noted in all dose groups of both species.

Benign neoplasms of pancreas and kidney were also observed in male rats (significant at low and mid doses, respectively), together with a morphological continuum of hyperplasia, which was regarded as a preneoplastic lesion. Incidences of hyperplasia were also significantly increased in females in these tissues without simultaneous increases in incidence of neoplasms. The preputial gland and the clitoral gland, as homologous organs in male and female rats, respectively, showed a significant increase in the combined incidences of adenomas or carcinomas for high-dose males and mid- and high-dose females. In female rats, adenocarcinomas of the mammary gland were dose-

dependently increased with a significant effect for the mid and high doses, whereas the incidence of fibro-adenomas decreased with increasing dose, even below control incidences (NTP, 1993; Irwin et al., 1995).

Tumour types uncommon in F344 rats were also observed. Carcinomas of the Zymbal's gland appeared in one female in the low-dose group and in three males and four females in high-dose groups (including interim sacrifice; significant effect). Adenomatous polyps or adenocarcinomas of the intestine occurred in two males and one female of the mid-dose group and three males and two females of the high-dose group. In view of the reduced number of animals at risk, both tumour types were considered to be possibly related to administration of 1,2,3-trichloropropane (NTP, 1993; Irwin et al., 1995).

Hepatocellular neoplasms were significantly increased in mid-dose (adenomas or carcinomas combined) and high-dose males and females (adenomas), accompanied by the induction of eosinophilic or basophilic liver foci. Incidences of Harderian gland adenomas of male and female mice as well as incidences of uterine stromal polyps, adenomas, or adenocarcinomas

Table 3: Incidence of non-neoplastic lesions and neoplasms after administration of 1,2,3-trichloropropane by gavage to female rats.^a

	Control	3 mg/kg body weight per day	10 mg/kg body weight per day	30 mg/kg body weight per day
Animals surviving to 104 weeks ^b (main study)	31/50	30/49	8/52	0/52
Mean survival (days)	649	654	580	366
Incidences of lesions and neoplasms (main + interim study)^{c,d,e}				
Oral mucosa	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Squamous cell papilloma	1	5	10**	21**
Squamous cell carcinoma	0	1	21**	23**
Forestomach	<i>60</i>	<i>59</i>	<i>59</i>	<i>60</i>
Hyperplasia, basal cell	0	10**	5*	9**
Hyperplasia, squamous	1	26**	15**	16**
Squamous cell papilloma	0	14**	37**	24**
Squamous cell carcinoma	0	3	9**	6**
Pancreas	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Hyperplasia	5	15*	24**	11**
Adenoma	0	0	2	0
Kidney	<i>60</i>	<i>57</i>	<i>60</i>	<i>59</i>
Hyperplasia	0	2	3	12**
Adenocarcinoma	0	0	0	1
Clitoral gland	<i>56</i>	<i>56</i>	<i>58</i>	<i>59</i>
Adenoma	5	11	14**	12*
Carcinoma	0	0	4	6
Adenoma or carcinoma	5	11	18**	17*
Mammary gland	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Fibroadenoma or adenoma	16	23	22*	2
Adenocarcinoma	1	6	12**	22**

^a From NTP (1993); Irwin et al. (1995).

^b The reduction in life span of the animals was caused by tumours induced by 1,2,3-trichloropropane.

^c Significantly different (* $P < 0.05$; ** $P < 0.01$) from controls by the life table test (squamous cell carcinoma and adenocarcinoma) or by logistic regression test (all other lesions).

^d Number of rats per group necropsied (oral mucosa or mammary gland) or with tissue examined microscopically (forestomach, pancreas, kidney, clitoral gland) given in italics.

^e Number of rats with lesion or neoplasm given in bold.

exceeding historical incidences were considered treatment-related (NTP, 1993; Irwin et al., 1995).

Among 140 carcinogenic chemicals tested in long-term animal studies, 1,2,3-trichloropropane was among the seven producing uterine neoplasms in mice (spontaneous tumour rate 0.3%) (Griesemer & Eustis, 1994). In a database comprising 536 carcinogens, only 12 substances, including 1,2,3-trichloropropane, produced uterine neoplasms in mice (Benigni & Pino, 1998).

The lower survival of certain study groups may explain the incongruities in certain dose-responses of tumour incidences between males and females and mid and high doses, e.g., for oral mucosa and forestomach neoplasms in rats. Reduced survival also reduced the number of animals at risk for the development of certain late-appearing tumour types (NTP, 1993; Irwin et al., 1995; La et al., 1996).

8.5 Genotoxicity and related end-points

A detailed description of *in vitro* and *in vivo* genotoxicity studies is given in MAK (1993) and IARC

(1995). 1,2,3-Trichloropropane was mutagenic to bacteria. Gene mutation, sister chromatid exchange, and chromosomal aberrations, but not DNA damage, were induced in rodent cells *in vitro*. In single studies, DNA binding and induction of DNA breaks, but not of dominant lethal mutations, were reported in rodents treated *in vivo* (IARC, 1995).

8.5.1 In vitro studies

1,2,3-Trichloropropane is mutagenic in bacterial test systems with *Salmonella typhimurium* strains TA 97, TA 100, and TA 1535 and *E. coli* WP₂ uvr A in the presence of metabolic activation (Dean & Brooks, 1979; Stolzenberg & Hine, 1980; Kier, 1982; Haworth et al., 1983; Ratpan & Plaumann, 1988; NTP, 1993; Låg et al., 1994). Some of these studies also reported an increase of revertants in *Salmonella* strains TA 98 (Kier, 1982; NTP, 1993) and TA 1537 (Dean & Brooks, 1979), while others found negative test results with one or both of these strains (Dean & Brooks, 1979; Kier, 1982; Haworth et al., 1983; Ratpan & Plaumann, 1988; NTP, 1993) as well as with TA 1538 (Dean & Brooks, 1979; Kier, 1982; Ratpan & Plaumann, 1988). However, only a

Table 4: Incidence of non-neoplastic lesions and neoplasms after administration of 1,2,3-trichloropropane by gavage to male mice.^a

	Control	6 mg/kg body weight per day	20 mg/kg body weight per day	60 mg/kg body weight per day
Animals surviving to 104 weeks ^b (main study)	42/51	18/51	0/54	0/56
Mean survival (days)	655	617	531	470
Incidences of lesions and neoplasms (main + interim study)^{c,d,e}				
Oral mucosa	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Squamous cell papilloma	0	0	0	2
Forestomach	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Hyperplasia, squamous	8	37**	32**	38**
Squamous cell papilloma	3	35**	25**	35**
Squamous cell carcinoma	0	41**	54**	55**
Liver	<i>60</i>	<i>59</i>	<i>60</i>	<i>60</i>
Hepatocellular adenoma	12	18	21*	31**
Hepatocellular carcinoma	4	11*	6	3
Harderian gland	60	59	60	60
Adenoma	1	2	10**	11**

^a From NTP (1993); Irwin et al. (1995).

^b The reduction in life span of the animals was caused by tumours induced by 1,2,3-trichloropropane.

^c Significantly different (* $P < 0.05$; ** $P < 0.01$) from controls by the life table test (squamous cell carcinoma) or the logistic regression test (all other lesions).

^d Number of mice per group necropsied (oral mucosa and Harderian gland) or with tissue examined microscopically (forestomach and liver) given in italics.

^e Number of mice with lesion or neoplasm given in bold.

Table 5: Incidence of non-neoplastic lesions and neoplasms after administration of 1,2,3-trichloropropane by gavage to female mice.^a

	Control	6 mg/kg body weight per day	20 mg/kg body weight per day	60 mg/kg body weight per day
Animals surviving to 104 weeks ^b (main study)	41/50	13/50	0/51	0/55
Mean survival (days)	661	601	515	453
Incidences of lesions and neoplasms (main + interim study)^{c,d,e}				
Oral mucosa	<i>60</i>	<i>60</i>	<i>60</i>	<i>60</i>
Squamous cell papilloma	1	0	1	0
Squamous cell carcinoma	0	0	1	5**
Forestomach	<i>60</i>	<i>60</i>	<i>60</i>	<i>60</i>
Hyperplasia, squamous	11	25**	23**	36**
Squamous cell papilloma	0	28**	27**	33**
Squamous cell carcinoma	0	47**	55**	51**
Liver	<i>60</i>	<i>60</i>	<i>60</i>	<i>60</i>
Hepatocellular adenoma	7	9	9	36**
Hepatocellular carcinoma	1	3	0	2
Harderian gland	<i>60</i>	<i>60</i>	<i>60</i>	<i>60</i>
Adenoma	3	6	7	10*
Uterus	<i>60</i>	<i>60</i>	<i>60</i>	<i>59</i>
Stromal polyp	0	2	2	7**
Adenoma	0	1	0	4
Carcinoma	0	4**	3**	8**
Adenoma or carcinoma	0	5**	3**	12**

^a From NTP (1993); Irwin et al. (1995).

^b The reduction in life span of the animals was caused by tumours induced by 1,2,3-trichloropropane.

^c Significantly different (* $P < 0.05$; ** $P < 0.01$) from controls by the life table test (squamous cell carcinoma and uterine adenocarcinoma) or the logistic regression test (all other lesions).

^d Number of mice necropsied (oral mucosa, Harderian gland, or uterus) or with tissue examined microscopically (forestomach and liver) given in italics.

^e Number of mice with lesion or neoplasm given in bold.

single publication points to a dose-dependent weak direct mutagenic activity of 1,2,3-trichloropropane in *S. typhimurium* TA 1535 (Dean & Brooks, 1979) in contrast to all other studies, despite comparable test conditions. The results demonstrate that 1,2,3-trichloropropane is a substance that, after metabolic activation, can cause both base pair substitution and frame shift mutation.

1,2,3-Trichloropropane (2 and 4 mmol/litre = 294 and 588 mg/litre) showed DNA breakage in human lymphocytes detected by a comet assay in both the presence and absence of S9 mix, but was negative in the micronucleus assay (2–8 mmol/litre = 294–1176 mg/litre) (Tafazoli et al., 1996, 1998; Anderson et al., 1998).

Studies in primary hepatocytes yielded negative test results for both the induction of DNA strand breaks (30–100 µmol/litre = 5–15 mg/litre; Holme et al., 1991) and unscheduled DNA synthesis (0.001% = 10 mg/litre; Williams et al., 1989).

Metabolic activation of 1,2,3-trichloropropane by S9 mix was a prerequisite to the induction of gene mutations in mouse lymphoma cells (Sawin & Hass, 1982; NTP, 1993), gene conversions in *Saccharomyces cerevisiae* (Dean & Brooks, 1979), sister chromatid exchange in CHO and V79 cells (von der Hude et al., 1987; NTP, 1993), chromosomal aberrations in CHO cells (NTP, 1993), and micronuclei in metabolically competent human lymphoblastoid cell lines (AHH-1, H2E1, and MCL-5) (Doherty et al., 1996; Parry et al., 1996). A chromosomal aberration test was negative with RL₁ rat liver cells (Dean & Brooks, 1979).

8.5.2 In vivo studies

DNA single strand breaks were detectable by alkaline elution as early as 60 min after one intraperitoneal injection of 1,2,3-trichloropropane, with LOAELs (significant effects) of 55 mg 1,2,3-trichloropropane/kg body weight in rat kidney (Låg et al., 1991) and 30 mg 1,2,3-trichloropropane/kg body weight in rat liver (Weber & Sipes, 1991).

A dominant lethal test demonstrated the absence of genotoxic activity in this special test (Saito-Suzuki et al., 1982).

Negative test results for a micronucleus test in mouse bone marrow (Douglas et al., 1985) and unscheduled DNA synthesis in rat hepatocytes *in vivo* (Mirsalis et al., 1983) mentioned in two abstracts cannot be validated because of lack of documentation (e.g., dose, test conditions).

Exposure of rats to 800 mg 1,2,3-trichloropropane/m³ for 1 week resulted in a disturbance of

hepatocyte mitosis. In a comparison of hepatocytes from control and exposed rats, there was a significant shift from binuclear cells to mononuclear polyploid cells. While binuclear diploid and tetraploid cells were significantly reduced in treated animals, mononuclear tetraploid and octaploid cells showed a significant corresponding increase, and cells with a ploidy of 16n appeared (Belyaeva et al., 1974).

Significant DNA adduct levels (as ¹⁴C equivalents of 1,2,3-trichloropropane) were measured in several target and non-target tissues 6 h after a single administration by gavage (La et al., 1995). One major adduct seemed to be formed. Dosages were 3 and 30 mg/kg body weight in male Fischer 344 rats and 6 and 60 mg/kg body weight in male B6C3F1 mice (low and high dosing of the carcinogenicity study [NTP, 1993]). In the rat, adduct levels ranged from 0.8 to 6.6 µmol/mol guanine and from 7.1 to 47.6 µmol/mol guanine for the low and high doses, respectively. The order of tissue adduct levels was kidney, liver, and pancreas > tongue and glandular stomach > forestomach > spleen. Adducts were not detectable in rat preputial gland or palate. In the mouse, adduct yields ranged from 0.32 to 28.1 µmol/mol guanine for the low dose and from 12.2 to 208.1 µmol/mol guanine for the high dose with the following ranking: glandular stomach > liver and forestomach > kidney > lung and spleen > brain, heart, and testes. Generally, there was a correlation between adduct formation and targets of tumorigenesis (see NTP, 1993). Targets for both end-points were forestomach and liver in mice and kidney, liver, pancreas, tongue, and forestomach in rats. Notable exceptions were relatively high DNA adduct concentrations in mouse glandular stomach and rat liver without corresponding tumours. Despite high tumour rates in palate and preputial gland of rats, no adducts were detectable, which was attributed to a lack of sensitivity of detection.

As the yields of DNA adducts from animals exposed to [¹⁴C]1,2,3-trichloropropane were not enough for structural characterization, 300 mg/kg body weight of the radiolabelled compound was administered intraperitoneally to rats. In the liver, the major DNA adduct was identified as S-[1-(hydroxymethyl)-2-(*N*⁷-guanyl)-ethyl]glutathione (La et al., 1995), confirming the role of GSH for adduct formation (Weber & Sipes, 1990, 1992). This *N*⁷-guanyl adduct may play a crucial role in the genotoxic activity of 1,2,3-trichloropropane, as corresponding adducts of other haloethyl GSH conjugates induced mutations at specific G:C base pairs in *Salmonella typhimurium*. Furthermore, the subsequent formation of abasic sites and reactive episulfonium ions is possible from such adducts (La et al., 1996).

Further investigations concentrated on the formation of this major adduct, S-[1-(hydroxymethyl)-2-(*N*⁷-

guanyl)ethyl]glutathione, and the induction of cell proliferation in male B6C3F1 mice in two target (forestomach and liver) and two non-target organs (glandular stomach and kidney) after repeated dosing of 6 mg 1,2,3-trichloropropane/kg body weight per day for 5 days either by gavage or by drinking-water. In comparison with the drinking-water exposure, the gavage bolus dose induced elevated concentrations of the DNA adduct (determination 24 h after last administration) in forestomach, liver, and kidney (significant effect for liver and kidney, approximately 2-fold), but not in glandular stomach. After a 2-week exposure (5 days/week), cell proliferation (BrdU incorporation in DNA) was increased in all four tissues relative to vehicle-treated control groups after the gavage exposure, but not after the drinking-water exposure. Significant differences between the two exposure routes were noted in glandular stomach at 18 h post-administration only, in kidney and liver at 30 h post-administration only, and in forestomach at both time points (La et al., 1996). It appears that the high local concentrations to be expected from the gavage bolus dose led to significant adduct formation and cell proliferation in contrast to the continuous but lower local concentrations resulting from drinking-water exposure (Swenberg et al., 1995; La & Swenberg, 1996; La et al., 1996).

8.6 Reproductive toxicity

8.6.1 Effects on fertility

In a study under the NTP's Continuous Breeding Protocol, 30, 60, or 120 mg 1,2,3-trichloropropane/kg body weight per day (doses chosen from results of a dose finding study: Task 1) was administered by gavage in corn oil to Swiss CD-1 mice (Gulati et al., 1990; Chapin et al., 1997). Twenty pairs per dose group and 40 pairs per control group were continuously exposed for a 7-day precohabitation and a 98-day cohabitation period to evaluate adverse effects on the F₀ generation and their litters (continuous breeding phase: Task 2). Subsequently, F₀ mice from control and high-dose groups were used in a cross-over mating trial to determine the sex affected by 1,2,3-trichloropropane treatment (Task 3: mating procedure control males × control females; control males × high-dose females; high-dose males × control females). For assessment of the fertility of the F₁ generation, Task 4 comprised a mating trial of F₁ mice from the last litters of Task 2, which had continuously been exposed to 1,2,3-trichloropropane during gestation, via lactation, and by gavage to the same concentrations as their parents from weaning to sexual maturity (about 74 days of age) and during a 7-day cohabitation period until delivery (duration of total study 28–30 weeks).

1,2,3-Trichloropropane treatment caused dose-related impairment of fertility in the absence of gross

general toxicity. In the high-dose group (120 mg 1,2,3-trichloropropane/kg body weight per day), fewer pairs of the F₀ generation delivered third, fourth, and fifth litters, and the litters had fewer live pups. Parental body weights were not decreased. In both male and female F₀ mice, liver weights were increased; female kidney and ovary weights were reduced; and epididymal weight was slightly reduced in the high-dose group. Testis weight and sperm parameters were unchanged. In the cross-over mating trial (Task 3), treated females mated to control males produced fewer live pups; no effect on fertility was found with treated males mated to control females. These data suggest an impairment of female fertility. The fertility index in the second-generation pups fed 1,2,3-trichloropropane was also significantly reduced. The number of pups trended lower at the high dose. In this generation (F₁), in contrast to the F₀ generation, the estrous cycle length was also increased at all three dose levels. The only conspicuous finding of the histopathological examination of selected organs in Task 3 was four cases of amyloidosis of the ovary among 10 treated females compared with 0/13 in the control group.

As only slight systemic toxicity was present, it can be concluded that 1,2,3-trichloropropane impairs fertility and reproduction at a dose level of 120 mg/kg body weight per day in both the parent and the offspring generations (Gulati et al., 1990). The cross-mating trial suggests slightly greater toxicity for the female than for the male reproductive system. As average estrous cycle lengths were significantly increased for all 1,2,3-trichloropropane-exposed females of the F₁ generation, the LOAEL for reproductive toxicity is 30 mg/kg body weight per day.

Other more limited studies that had been performed previously showed mostly negative results. This may be due to poor study design or problems during the study.

In a one-generation reproduction/fertility study, CD rats (10 males and 20 females per group) were exposed to 0, 3.1, or 9.2 mg/m³ (Johannsen et al., 1988) for 6 h/day, 5 days/week, over a pre-mating period of 10 weeks, the mating period of up to 40 days for both sexes, and the gestation period of 14 days (days 0 through 14) for females only. Females of the F₀ generation and offspring were evaluated during a 21-day lactation period. No treatment-related effects on the parent generation or on reproductive parameters were observed (Johannsen et al., 1988). In a previous study (Bio/dynamics Inc., 1980; Johannsen et al., 1988) using 0, 27.5, and 92 mg 1,2,3-trichloropropane/m³, the weights and the histopathological examination of gonads of the F₀ generation revealed no adverse effects of 1,2,3-trichloropropane exposure on testes, epididymides, or ovaries; however, in view of the poor mating performance, only limited conclusions on 1,2,3-

trichloropropane-related effects on fertility and reproduction are possible.

Fifteen male Sprague-Dawley rats treated with 80 mg 1,2,3-trichloropropane/kg body weight per day for 5 days by gastric intubation (vehicle olive oil) during a dominant lethal study showed no impairment of mating performance and no meaningful changes in the indices measured, such as numbers of implants, live embryos, and dead implants (Saito-Suzuki et al., 1982).

Male rats administered 1,2,3-trichloropropane by gavage at a dosage of 125 mg/kg body weight per day for 120 days showed significant increases in relative testes weights after 8 and 17 weeks of administration and a significant decrease in relative epididymis weight at the 8-week time point only. However, no effects on sperm count or sperm morphology and no histomorphological changes of testes or epididymis were observed (Hazleton Laboratories America Inc., 1983a). Similarly treated mice showed differences in numbers of sperm per milligram cauda of epididymis, which were considered to be of questionable significance in view of the absence of any significant findings on weights of testes or epididymis or any histopathological findings (Hazleton Laboratories America Inc., 1983b).

8.6.2 Developmental toxicity

Sprague-Dawley rats were exposed to 37 mg 1,2,3-trichloropropane/kg body weight in corn oil (determined as the maximum tolerable dose in dose-response studies) by daily intraperitoneal injection from gestation days 1 to 15 and sacrificed on gestational day 21. Maternal toxicity was apparent in the absence of any fetotoxic or teratogenic effects. These results cannot be validated, as details of the test results are not specified in the review article (Hardin et al., 1981).

In addition to these data, reproduction studies by the inhalation route (Johannsen et al., 1988) or by the oral route (Gulati et al., 1990; Chapin et al., 1997) found no external malformation or fetal toxicity effects on the F₀ offspring.

8.7 Other toxicity / mode of action

The endogenous formation of reactive intermediates from 1,2,3-trichloropropane plays a crucial role in the organotoxic, genotoxic, and carcinogenic action of 1,2,3-trichloropropane. The postulated formation of alkylating species is consistent with the presence of covalently bound radioactivity in liver and kidney and in target tissues of carcinogenic action after gavage administration of [¹⁴C]1,2,3-trichloropropane. Significant DNA adduct levels (as ¹⁴C equivalents of 1,2,3-trichloropropane) were found in forestomach and liver in mice and in kidney, liver, pancreas, tongue, and forestomach

in rats (Weber & Sipes, 1990; La et al., 1995). A predominant role was assigned to episulfonium ions formed *in situ* during the metabolism of 1,2,3-trichloropropane in the liver and from processing of GSH conjugates of 1,2,3-trichloropropane in the kidney, leading to hepatotoxic and nephrotoxic lesions (NTP, 1993).

A further publication, in abstract form only without detailed documentation of test conditions and results, presented a new hypothesis for the formation of forestomach tumours (Ito et al., 1996). According to these investigations, analysis of *ras* mutations in forestomach tumours of mice from the NTP (1993) study showed that the observed mutations are not consistent with the miscoding properties of the major DNA adduct S-[1-(hydroxymethyl)-2-(N⁷-guanyl)ethyl]glutathione that had formerly been identified in various tissues by the same working group (La et al., 1995, 1996). Preliminary studies suggested that 1,2,3-trichloropropane administration produced increases in the etheno DNA adducts 1,N⁶-ethenodeoxyadenosine and 3,N⁴-ethenodeoxycytidine, which are thought to arise endogenously from lipid oxidation. The resulting alternative hypothesis for the formation of forestomach tumours is an indirect mutagenic effect of 1,2,3-trichloropropane by GSH depletion as a consequence of the bolus application by gavage, which may induce lipid oxidation. Consequently, GSH plays a crucial role in adduct formation, being involved both in the formation of the major DNA adduct S-[1-(hydroxymethyl)-2-(N⁷-guanyl)ethyl]glutathione and in the initiation of lipid oxidation (Ito et al., 1996).

Studies on possible mechanisms of 1,2,3-trichloropropane-induced carcinogenesis have shown that DNA adduct formation in male B6C3F1 mice approximately doubled after administration of 6 mg 1,2,3-trichloropropane/kg body weight per day for 1 week by gavage compared with administration of the same dose via drinking-water. Further, only gavage exposure led to a significant increase in cell proliferation rate compared with administration in drinking-water (La et al., 1996). It appears that the high local concentrations to be expected from the gavage bolus dose led to significant adduct formation and cell proliferation, in contrast to the continuous but lower local concentrations resulting from drinking-water exposure. Consequently, it has to be expected that gavage exposure will overestimate the carcinogenic potency of 1,2,3-trichloropropane (Swenberg et al., 1995; La & Swenberg, 1996; La et al., 1996). A number of chemicals, including the structurally related 1,2-dibromo-3-chloropropane, are also known to induce high incidences of forestomach tumours, but only when administered via gavage (La et al., 1996).

9. EFFECTS ON HUMANS

After a 15-min exposure of 12 persons to 1,2,3-trichloropropane vapours, a concentration of 610 mg/m³ was described as an irritant to eyes and throat (insufficient documentation) (Silverman et al., 1946).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

1,2,3-Trichloropropane may enter the hydrosphere due to its production, use, and application. However, it can evaporate from the aqueous phase to some extent, thus reducing the exposure concentration for aquatic species. Such loss due to evaporation of 1,2,3-trichloropropane from the aqueous phase was demonstrated in a recent study simulating a 48-h *Daphnia magna* open vessel test (Solvay, 2001b). Therefore, long-term toxicity tests performed with this compound should account for this potential loss by employing a test design that maintains constant exposure, thus improving the reliability of data obtained.

Several tests have been performed to establish the acute toxicity of 1,2,3-trichloropropane to freshwater biota representing different trophic levels, and these are summarized in Table 6. Most of these studies are of limited value, because initial concentrations of 1,2,3-trichloropropane were not measured and losses of 1,2,3-trichloropropane due to volatilization were not taken into account over the tests' duration.

Use of closed test systems to reduce these losses has recently been reported for two tests with the microalga *Selenastrum capricornutum* and the cladoceran *Daphnia magna* (Solvay, 2001a, 2002).

The acute toxicity of 1,2,3-trichloropropane to *Daphnia magna* (end-point = immobilization after 48 h) was determined in closed glass flasks following OECD guideline 202 (Solvay, 2002). 1,2,3-Trichloropropane concentrations in the test flasks were determined by gas chromatography at the beginning and end of the test. Losses of 1,2,3-trichloropropane over the 48-h test duration ranged from 6 to 32%; therefore, the mean measured concentrations (0, 2.5, 4.7, 8.4, 15, and 27 mg/litre) were used to calculate the toxicity test end-points. No test concentrations gave partial immobility; therefore, the 48-h EC₅₀ was estimated to be 20 mg/litre (95% confidence interval of 15–27 mg/litre), with a no-observed-effect concentration (NOEC) of 15 mg/litre.

Assays performed by Blum & Speece (1991) employing methanogens (end-point = inhibition of gas production), aerobic heterotrophic bacteria (end-point = inhibition of oxygen uptake), *Nitrosomonas* sp. (end-point = inhibition of ammonia consumption), and *Photobacterium phosphoreum* (end-point = inhibition of bioluminescence) showed that the methanogens exhibited the lowest IC₅₀ value of 0.63 mg/litre.

The most sensitive of three algal species tested was *Selenastrum capricornutum*, with a 72-h E_BC₅₀ value of 49.6 mg/litre (end-point = inhibition of biomass formation) and a 72-h E_RC₅₀ value of 101 mg/litre (end-point = inhibition of growth rate; Solvay, 2001a).

For those invertebrates tested, the lowest EC₅₀ value of 4.1 mg/litre (end-point = immobilization) — which was in fact several-fold lower than the corresponding values reported for *Daphnia magna* — was reported by Rose et al. (1998) for the cladoceran *Ceriodaphnia* cf. *dubia*. Possible reasons for this apparently higher sensitivity, such as differences in experimental conditions, water chemistry, or organism size to test volume ratio, were excluded by these authors. They advocate that the variation in sensitivity was probably due to an inherent sensitivity or to the dissimilar size of the different species.

From studies relating to the long-term toxicity of 1,2,3-trichloropropane and using the invertebrate *Chaetogammarus marinus*, Kooijman (1981) reported as the lowest value a 21-day LC₅₀ of 20 mg/litre.

In toxicity studies conducted with several fish species, the lowest LC₅₀ value (7-day incubation) was established for guppies (*Poecilia reticulata*) as 41.6 mg 1,2,3-trichloropropane/litre (Könemann, 1981). For *Oncorhynchus mykiss* (ABC, 1986c), the lowest estimated NOEC (96 h) value was <10 mg/litre.

10.2 Terrestrial environment

Walton et al. (1989) investigated the effect of a nominal concentration of 1000 mg 1,2,3-trichloropropane/kg soil upon the microbial activity in two different soils (silty and sandy loam) by measuring soil respiration as an indicator for microbial activity. They found a reduction of carbon dioxide production of 0.09 and 0.18 µg/g soil per day after day 4 for silty and sandy loam, respectively. However, after 6 days of incubation, no significant difference between treated soils and controls was detectable. These results indicate a low toxicity potential of 1,2,3-trichloropropane for the terrestrial environment. Studies on the toxicity of 1,2,3-trichloropropane to terrestrial invertebrates or vertebrates or on effects on ecosystems are not available. However, employing ECOSAR Version 0.99g (a structure–activity

Table 6: Aquatic toxicity of 1,2,3-trichloropropane.

Species tested (reported test method)	End-point (effect)	Concentration ^a (mg/litre)	Reference
Bacteria			
Mixed culture of aerobic heterotrophs (inhibition of oxygen uptake)	15-h IC ₅₀	290 (nominal)	Blum & Speece (1991)
<i>Nitrosomonas</i> sp. (inhibition of ammonia consumption)	24-h IC ₅₀	30 (nominal)	Blum & Speece (1991)
<i>Photobacterium phosphoreum</i> (inhibition of bioluminescence)	5-min IC ₅₀	19 (nominal)	Blum & Speece (1991)
Methanogens (not characterized) (inhibition of gas production)	48-h IC ₅₀	0.63 (nominal)	Blum & Speece (1991)
Green algae			
<i>Chlorella vulgaris</i> (inhibition of carbon dioxide uptake)	3-h EC ₅₀	170 (nominal)	Hutchinson et al. (1980)
<i>Chlamydomonas angulosa</i> (inhibition of carbon dioxide uptake)	3-h EC ₅₀	112 (nominal)	Hutchinson et al. (1980)
<i>Selenastrum capricornutum</i> (inhibition of biomass production and growth rate)	72-h E _B C ₅₀	49.6 (effective ^b)	Solvay (2001a) ^c
	72-h E _R C ₅₀	101 (effective ^b)	
	72-h NOEC	12.8 (effective ^b)	
Invertebrates			
<i>Chaetogammarus marinus</i> (mortality)	48-h LC ₅₀	60 (not specified)	Kooijman (1981)
	96-h LC ₅₀	45 (not specified)	
	21-day LC ₅₀	20 (not specified)	
<i>Daphnia magna</i> (immobilization, static, unfed)	48-h IC ₅₀	35 (nominal)	Hermens et al. (1984)
<i>Daphnia magna</i> (mortality and abnormal effects, static, fed)	24-h LC ₅₀	41 (nominal)	ABC (1986a)
	48-h LC ₅₀	20 (nominal)	
<i>Daphnia magna</i> (immobilization)	48-h EC ₅₀	20 (effective ^b)	Solvay (2002)
	48-h NOEC	15 (effective ^b)	
<i>Ceriodaphnia</i> cf. <i>dubia</i> (immobilization)	48-h EC ₅₀	4.1 (nominal)	Rose et al. (1998)
Vertebrates			
Japanese medaka (<i>Oryzias latipes</i>) (mortality)	48-h LC ₅₀	109 (nominal)	MITI (1992)
Bluegill sunfish (<i>Lepomis macrochirus</i>) (mortality, abnormal effects)	24-h LC ₅₀	75 (nominal)	ABC (1986b)
Rainbow trout (<i>Oncorhynchus mykiss</i>) (mortality, abnormal effects)	24-h LC ₅₀	75 (nominal)	ABC (1986c)
	48-h LC ₅₀	64 (nominal)	
	96-h LC ₅₀	42 (nominal)	
	96-h NOEC	<10 (nominal)	
Fathead minnow (<i>Pimephales promelas</i>) (mortality)	96-h LC ₅₀	66.5 (effective ^b)	Geiger et al. (1990)
Guppy (<i>Poecilia reticulata</i>) (mortality)	7-day LC ₅₀	41.6 (not specified)	Könemann (1981)

^a As 1,2,3-trichloropropane can evaporate from the aqueous phase (only recently demonstrated in studies simulating a 48-h *Daphnia magna* test in open vessels; Solvay, 2001b), which would therefore reduce the concentration of the test compound over time, we specified (in parentheses) whether the values given were based upon nominal (initial concentrations) or effective (loss of compound checked and accounted for) concentrations.

^b In these studies, end-points reported were based on mean measured 1,2,3-trichloropropane concentrations.

^c Performed according to OECD guideline 201.

relationship program provided by the US EPA that is used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured) and the measured physicochemical properties of 1,2,3-trichloropropane (relative molecular mass 147.43, log K_{ow} 2.27, melting point -14.7 °C, water solubility 1750 mg/litre, ECOSAR class neutral organics), a 14-day LC₅₀ value of about 640 mg/kg dry weight soil for earthworm toxicity can be estimated.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

Data on the effects on humans are limited to the description of an irritant action on mucous membranes.

1,2,3-Trichloropropane is a multisite carcinogen in both rats and mice, even at the lowest dose, when administered in corn oil via gavage in dosages of 0, 3, 10, and 30 mg/kg body weight per day to F344/N rats and 0, 6, 20, and 60 mg/kg body weight per day to

B6C3F1 mice for 5 days weekly (NTP, 1993; Irwin et al., 1995).

Main targets of carcinogenic action are the forestomach and the oral mucosa in rats of both sexes, the mammary gland in female rats, pancreas and kidney in male rats, as well as the preputial gland and clitoral gland, as homologous organs in male and female rats, respectively. Mice responded with neoplasms of the forestomach, the liver, and the Harderian gland. Uncommon tumour types were reported, such as carcinomas of the Zymbal's gland and adenomatous polyps or adenocarcinomas of the intestine in rats and uterine neoplasms in mice (NTP, 1993; Irwin et al., 1995). Considering the very high incidences of forestomach neoplasms in low-dose groups of rats (33–66%) and mice (nearly 100%), this carcinogenic activity might have been detected even at lower doses, and the LOAELs for significantly increased tumour incidences will be well below 3 mg/kg body weight per day in rats and 6 mg/kg body weight per day in mice.

1,2,3-Trichloropropane was mutagenic to bacteria. Gene mutation, sister chromatid exchange, and chromosomal aberrations, but not DNA damage, were induced in rodent cells *in vitro*. *In vivo*, DNA single strand breaks were detectable by alkaline elution, whereas genotoxic action in a dominant lethal test was absent.

The DNA adduct *S*-[1-(hydroxymethyl)-2-(*N*⁷-guanyl)ethyl]glutathione was identified in preneoplastic and neoplastic lesions of target organs.

When 1,2,3-trichloropropane was administered to Sprague-Dawley rats via drinking-water for 13 weeks, the LOAELs for moderate hepatotoxic and nephrotoxic effects were 17.6 mg/kg body weight per day for female rats and 113 mg/kg body weight per day for male rats (Villeneuve et al., 1985).

Repeated inhalation exposure of F344 rats and B6C3F1 mice to 1,2,3-trichloropropane resulted in cytotoxic action in the upper respiratory tract, lung, and liver. Based on the most sensitive end-point — i.e., changes in the olfactory epithelium detectable by histopathological examination of nose tissue — the overall NOAEL was 6 mg/m³ for rats and 18 mg/m³ for mice derived from an 11-day inhalation study (Miller et al., 1986b).

The results of a two-generation study in Swiss mice showed that 1,2,3-trichloropropane impaired fertility and reproduction at a dose level of 120 mg/kg body weight per day (administered via gavage) in both the parent and the offspring generations in the presence of only slight systemic toxicity (Gulati et al., 1990; Chapin et al., 1997). A cross-mating trial suggested greater toxicity for the female than for the male reproductive system. The

average estrous cycle length was significantly increased for all 1,2,3-trichloropropane-exposed females of the F₁ generation, with the lowest dose being 30 mg/kg body weight per day. Developmental toxicity has not been reported, but the data are very limited.

11.1.2 **Criteria for setting tolerable intakes and tolerable concentrations for 1,2,3-trichloropropane**

Based on studies in animals, critical effects of 1,2,3-trichloropropane are irritation (dermal, inhalation) and cancer. Following inhalation exposure, respiratory tract irritation has been observed in rats at concentrations in the range of a few milligrams per cubic metre.

1,2,3-Trichloropropane is carcinogenic in rats and mice, inducing a wide range of tumours in both sexes. In the NTP gavage carcinogenicity studies, the reduction in life span of the animals was caused by tumours induced by 1,2,3-trichloropropane. Data on mode of action, including studies on metabolism, genotoxicity, and determination of DNA adduct formation, suggest that the mechanism of induction of tumours involves direct interaction of an active metabolite with genetic material. Hence, exposure to 1,2,3-trichloropropane should be avoided.¹

While a tolerable concentration or tolerable intake has not been derived here, it should be noted that the tumorigenic potency of this compound is high, with tumours being observed at doses as low as 3 mg/kg body weight per day in rats following gavage administration.

The NTP gavage studies were chosen as key studies, as the drinking-water study was only of 13 weeks' duration and relatively moderate changes were observed.

11.1.3 **Sample risk characterization**

11.1.3.1 *Estimated population exposure*

There is a lack of information on present-day uses of 1,2,3-trichloropropane. Older reports suggest that it has a use as a solvent and extractive agent, paint and varnish remover, and cleaning and degreasing agent. If so, then there could be widespread dermal and inhalation exposure for both occupational and general populations.

There are no data from such exposures, so estimations have been made from the scarce data available on concentrations in ambient and indoor air and drinking-

¹ The source document does not include derivation of a guidance value for 1,2,3-trichloropropane, a genotoxic carcinogen. In CICADs, a tolerable intake or tolerable concentration may be developed (independent of the source document) for genotoxic chemicals, to indicate the risk level at a particular dose; in this instance, however, this was not done.

water. The data on high exposures in air in Kuwait cannot be ignored, but there is no obvious explanation for them. Likewise, the value given for daily intake of 1,2,3-trichloropropane from food has not been substantiated.

Assuming a daily intake of 7.4 µg in food, a daily consumption of 2 litres of drinking-water containing 0.1 µg 1,2,3-trichloropropane/litre, a daily intake of 20 m³ air with an average load of 0.1 µg 1,2,3-trichloropropane/m³, and a body weight of 64 kg, a daily intake of 150 ng/kg body weight can be estimated (34 ng/kg body weight if the questionable food intake is not included).

Using the above assumptions but the reported much higher values for air in Kuwait (outdoor air 491 µg/m³; indoor air 2480 µg/m³) and assuming that 50% of the time is spent outdoors and 50% indoors, one can calculate a daily uptake of about 464 µg/kg body weight (nearly 0.5 mg/kg body weight per day).

Data on occupational exposure (Brock & Carroll, 1985) suggest a maximum short-term maintenance personnel exposure concentration of 17 mg 1,2,3-trichloropropane/m³ for a chemical plant in the USA. However, exposure concentrations in other workplaces did not usually exceed 0.61 mg/m³.

These workplace concentrations (workday situation: daily consumption of 20 m³ air, accrued 1-h peak concentration with 17 mg/m³, 7-h on-site ambient air with <0.61 mg/m³, remaining time ambient air with 0.1 µg/m³; intake via food and drinking-water not accounted for) give an intake of up to 277 µg/kg body weight per day, i.e., nearly 0.3 mg/kg body weight per day (compared with 3 mg/kg body weight per day for the rat carcinogenicity study).

11.1.3.2 Health risks induced by the exposure

Tumours occurred in rats and mice, even at the lowest dose; therefore, we do not have a no-effect level to compare with human population exposure. This makes a sample risk assessment problematic. However, it can be said that the mechanics for occupationally exposed persons above (0.3 mg/kg body weight per day) and for non-occupationally exposed persons exposed to concentrations as supposed by the Kuwaiti data (nearly 0.5 mg/kg body weight per day) suggest that these populations may have a higher risk of cancer than those exposed only to 1,2,3-trichloropropane in drinking-water and ambient air levels other than those cited in Kuwait (34 ng/kg body weight per day).

11.1.4 Uncertainties in the hazard characterization

There is a lack of information on present uses and therefore on a general population exposure scenario.

There was only one report on occupational exposure to 1,2,3-trichloropropane, and this was not recent and could not be substantiated by other data.

Although there is likely to be widespread human exposure to 1,2,3-trichloropropane in polymer manufacture and when the chemical is used as a solvent for degreasing and paint stripping, there is a lack of information on dermal exposure.

Risk assessment may be affected by differences in the routes of exposure. Marked differences in toxicity have been reported between rats administered 1,2,3-trichloropropane in drinking-water (Villeneuve et al., 1985) and rats exposed by gavage (NTP, 1993). Hepatotoxicity, nephrotoxicity, and nasal and respiratory toxicity were observed after gavage administration (125 mg/kg body weight per day for 17 weeks), whereas increases in liver weight and mild histological lesions were observed when the chemical was administered in drinking-water (up to 113 mg/kg body weight per day for 9 days). However, it should be noted that the drinking-water study was only for 9 days' administration. A 2-year drinking-water study was not available. However, 1,2,3-trichloropropane was found to induce up to 2.4 times more DNA adducts in mice via gavage than by drinking-water in a comparable exposure (6 mg/kg body weight per day) (La et al., 1996).

It is not known how relevant forestomach tumours after gavage administration in rats are for human risk assessment, as humans do not have this organ. However, there were tumours at other sites.

There is some uncertainty as to the relevance of changes in olfactory epithelium in rats. Rodents are obligate nasal breathers, so the significance of these changes remains unclear when extrapolating to humans and other species. However, the olfactory epithelium was also a target of the cytotoxic action of 1,2,3-trichloropropane after gavage application to rats for 17 weeks.

Further research is necessary to determine if 1,2,3-trichloropropane exposure is selecting the sex of offspring in favour of females (Gulati et al., 1990; Chapin et al., 1997).

11.2 Evaluation of environmental effects

11.2.1 Aquatic environment

The main environmental target compartments of 1,2,3-trichloropropane are air and water, where this compound is only slowly transformed by abiotic reactions and poorly transformed aerobically by microorganisms. Therefore, conditions not accelerating biotic or abiotic removal might lead to the presence of detectable concentrations of this compound in these two compartments. However, a reliable quantification of 1,2,3-trichloropropane currently released from all industrial sources is impossible with the data available.

The experimentally determined bioconcentration data as well as the measured $\log K_{ow}$ value indicate a low bioaccumulation potential for 1,2,3-trichloropropane.

A sample risk characterization according to the European Commission (EC, 1996) with respect to the aquatic environment might be performed by calculating the ratio between a local PEC (based on measured data) and a corresponding PNEC.

Although a quantification of 1,2,3-trichloropropane released into the environment is not possible with data currently available, recent monitoring data from northern Europe might be regarded as representative for an industrialized region. The highest reported value for Dutch surface water of the rivers Rhein, Meuse, and Westerscheldt and the Northern Delta Area is 2.2 $\mu\text{g}/\text{litre}$, which can be employed as the local PEC. A corresponding PNEC for surface water might be estimated from the lowest EC_{50} value from tests carried out in closed systems to minimize 1,2,3-trichloropropane losses. The 48-h EC_{50} value for *Daphnia magna* immobilization (20 mg/litre) was used to derive the PNEC, together with an uncertainty factor of 1000 (EC, 1996): $\text{PNEC} = 20 \text{ mg/litre} \div 1000 = 0.02 \text{ mg/litre}$. Although a lower value was obtained for *Ceriodaphnia cf. dubia* (48-h EC_{50} of 4.1 mg/litre), this test was based on nominal concentrations only and therefore was not used in the risk characterization.

Using the highest recently measured concentration of 1,2,3-trichloropropane in surface water, the hazard quotient (PEC/PNEC) becomes $2.2 \mu\text{g}/\text{litre} \div 20 \mu\text{g}/\text{litre} = 0.11$. Because this is less than 1, no further information, testing, or risk reduction measures are required.

11.2.2 Terrestrial environment

1,2,3-Trichloropropane will preferably partition into air (about 85%) and water (about 11%) and only to a limited extent into soil (the remaining 4%) (Mackay et al., 1993).

The determined soil sorption coefficients indicate a low potential for soil sorption. Therefore, under conditions not promoting abiotic or biotic transformation, leaching of 1,2,3-trichloropropane into groundwater can take place.

As only inhibition tests on soil-bound microbial activity are available, it does not appear appropriate to employ these limited data for a risk characterization. Valid studies on the toxicity of 1,2,3-trichloropropane to terrestrial invertebrates or vertebrates are not available.

11.2.3 Uncertainties in the evaluation of environmental effects

The acute toxicity of 1,2,3-trichloropropane was tested using a variety of species from different trophic levels. However, the number of data is still limited. Because 1,2,3-trichloropropane is volatile, only acute toxicity data based on measured concentrations were used in the risk characterization. However, it is likely that the true concentrations in the other tests were much lower than the nominal concentrations, so that the reported NOEC and $\text{LC}_{50}/\text{EC}_{50}$ values are too high (i.e., the toxicity of 1,2,3-trichloropropane is greater than that estimated from the acute toxicity tests). If the true PNEC is lower based on measured concentrations, then the calculated PEC:PNEC ratio may be 1 or higher, indicating that the risk is higher than that determined in section 11.2.1. Until further testing is carried out with additional species using closed test systems, the results of the risk characterization outlined here should be interpreted with caution.

For the terrestrial compartment, the available toxicity studies measuring the inhibition of soil-bound microbial activity by 1,2,3-trichloropropane cannot be regarded as sufficient to support a quantitative risk characterization.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

There is inadequate evidence in humans for the carcinogenicity of 1,2,3-trichloropropane. There is sufficient evidence in experimental animals for the carcinogenicity of 1,2,3-trichloropropane. IARC (1995) classifies 1,2,3-trichloropropane as a Group 2A carcinogen: probably carcinogenic to humans.

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APPENDIX 1 — SOURCE DOCUMENTS

BUA (1993) 1,2,3-Trichloropropane. German Chemical Society (GDCh) Advisory Committee on Existing Chemicals of Environmental Relevance (BUA). Stuttgart, Hirzel, pp. 1–97 (BUA Report 154).

For the BUA review process, the company that is in charge of writing the report (usually the largest producer in Germany) prepares a draft report using literature from an extensive literature search as well as internal company studies. This draft is subject to a peer review in several readings of a working group consisting of representatives from government agencies, the scientific community, and industry.

The English translation of this report was published in 1997.

MAK (1993) 1,2,3-Trichloropropane. In: Greim H, ed. *Occupational toxicants: critical data evaluation for MAK values and classification of carcinogens. Vol. 9. Deutsche Forschungsgemeinschaft (DFG); Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK). Weinheim, Wiley-VCH, pp. 171–192.*

The scientific documentations of the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK) are based on critical evaluations of the available toxicological and occupational medical data from extensive literature searches and from well documented industrial data. The evaluation documents involve a critical examination of the quality of the database, indicating inadequacy or doubtful validity of data and identification of data gaps. This critical evaluation and the classification of substances are the result of an extensive discussion process by the members of the Commission, proceeding from draft documentation prepared by members of the Commission, by ad hoc experts, or by the Scientific Secretariat of the Commission. Scientific expertise is guaranteed by the members of the Commission, which consists of experts from the scientific community, industry, and employer associations.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 1,2,3-trichloropropane was sent for review to IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

J.E. Andrews, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

R. Benson, Drinking Water Program, US Environmental Protection Agency, Denver, CO, USA

R.S. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

M. Cikrt, National Institute of Public Health, Prague, Czech Republic

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F. Simeonova, Center of Hygiene, Medical Ecology and Nutrition, Sofia, Bulgaria

E. Soderlund, Norwegian Public Health Institute, Oslo, Norway

J. Stauber, Centre for Advanced Analytical Chemistry, Bangor, Australia

J.M.H. Temmink, Wageningen Agricultural University, Wageningen, Netherlands

K. Ziegler-Skylakakis, European Commission, Luxembourg

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Monks Wood, United Kingdom
16–19 September 2002

Members

Dr R. Benson, US Environmental Protection Agency, Region VIII, Denver, CO, USA

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APPENDIX 4 — ABBREVIATIONS AND ACRONYMS

ACPC	<i>N</i> -acetyl- <i>S</i> -(3-chloro-2-hydroxypropyl)- <i>L</i> -cysteine
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CICAD	Concise International Chemical Assessment Document
CPC	<i>S</i> -(3-chloro-2-hydroxypropyl)- <i>L</i> -cysteine
DCA	1,3-dichloroacetone
DNA	deoxyribonucleic acid
EC ₅₀	median effective concentration
ECD	electron capture detection
ELCD	electrolytic conductivity detection
EPA	Environmental Protection Agency (US)
FID	flame ionization detection
GC	gas chromatography
GMA	2-(<i>S</i> -glutathionyl)malonic acid
GSH	glutathione
IC ₅₀	median inhibitory concentration
ICSC	International Chemical Safety Card
<i>K</i> _{oc}	sorption coefficient
LC ₅₀	median lethal concentration
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MS	mass spectrometry
NADH	nicotinamide adenine dinucleotide, reduced form
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NTP	National Toxicology Program (US)
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PID	photoionization detection
PNEC	predicted no-effect concentration
RNA	ribonucleic acid
SI	International System of Units (Système international d'unités)
SPI	The Society of the Plastics Industry
WHO	World Health Organization

1,2,3-TRICHLOROPROPANE

0683

October 2002

CAS No: 96-18-4

RTECS No: TZ9275000

UN No: 2810

EC No: 602-062-00-X

Glycerol trichlorohydrin

Allyl trichloride

 $C_3H_5Cl_3$ / $CH_2ClCHClCH_2Cl$

Molecular mass: 147.4

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 74°C explosive vapour/air mixtures may be formed. Risk of fire and explosion on contact with metals.	Above 74°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Cough. Sore throat. Headache. Drowsiness. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Artificial respiration may be needed. Refer for medical attention.
Skin	Dry skin. Redness. Prickling.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain.	Safety spectacles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Nausea. Headache. Vomiting. Diarrhoea. Drowsiness. Unconsciousness.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Give plenty of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: filter respirator for organic gases and vapours.)	Xn Symbol R: 20/21/22 S: (2-)37/39 Note: D UN Hazard Class: 6.1 UN Pack Group: III Marine pollutant.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-61GT1-I NFPA Code: H3; F2; R0	Separated from metals. Cool. Keep in a well-ventilated room.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

Physical dangers

The vapour is heavier than air.

Chemical dangers

The substance decomposes on burning producing toxic and corrosive fumes. Reacts violently with metals causing explosion hazard.

Occupational exposure limits

TLV: 10 ppm as TWA; (skin); A3; (ACGIH 2002).

MAK: Carcinogen category: 2; (DFG 2002).

Routes of exposure

The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

Inhalation risk

A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

Effects of short-term exposure

The substance is irritating to the eyes and the respiratory tract. The substance may cause effects on the liver and kidneys, resulting in impaired functions. Exposure at high concentrations may result in unconsciousness.

Effects of long-term or repeated exposure

This substance is probably carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 156°C

Melting point: -14°C

Relative density (water = 1): 1.4

Solubility in water: none

Vapour pressure, kPa at 20°C: 0.29

Relative vapour density (air = 1): 5.1

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.01

Flash point: 74°C

Auto-ignition temperature: 304°C

Explosive limits, vol% in air: 3.2-12.6

Octanol/water partition coefficient as log Pow: 2.27

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms. This substance may be hazardous to the environment; special attention should be given to ground water contamination.

NOTES

Do NOT take working clothes home.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

RÉSUMÉ D'ORIENTATION

Le présent CICAD consacré au 1,2,3-trichloropropane a été préparé par l'Institut Fraunhofer de toxicologie et de recherche sur les aérosols (Secteur recherche pharmaceutique et inhalation clinique), de Hanovre (Allemagne). Il s'inspire de rapports établis par le Comité consultatif de la Société allemande de chimie sur les substances chimiques d'importance écologique (BUA, 1993) et par la Commission allemande pour l'étude des risques écologiques imputables aux composés chimiques sur le lieu de travail (MAK, 1993). Il a été procédé à un dépouillement bibliographique exhaustif des bases de données correspondantes, en novembre 2001 pour les effets sanitaires et en septembre 2002 pour les effets environnementaux, afin de rechercher toute référence intéressante à des publications postérieures aux rapports en question. Des informations sur la préparation et l'examen par des pairs des sources documentaires utilisées sont données à l'appendice 1. L'appendice 2 fournit des renseignements sur l'examen par des pairs du présent CICAD. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Monks Wood (Royaume-Uni) du 16 au 19 septembre 2002. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique du 1,2,3-trichloropropane (ICSC 0683), établie par le Programme international sur la sécurité chimique (IPCS, 1999), est également reproduite dans le présent document.

Le 1,2,3-trichloropropane (No CAS 96-18-4), est un alcane chloré. Indépendamment de sa préparation industrielle, il se forme également en quantités notables comme sous-produit de la synthèse d'autres dérivés chlorés, notamment de l'épichlorhydrine. On l'utilise comme intermédiaire dans la synthèse d'autres composés (des pesticides, par exemple) et comme agent de réticulation pour la préparation de certains polymères comme les polysulfures et le polyhexafluoropropylène. Dans certains rapports plus anciens, le 1,2,3-trichloropropane est décrit comme un solvant des composés et résines hydrophobes, un dissolvant pour peintures et vernis et un agent de dégraissage.

Le compartiment de l'environnement où aboutit principalement le 1,2,3-trichloropropane libéré dans le milieu est l'air atmosphérique (à hauteur d'environ 85 %), suivi par l'eau (environ 11 %). Les concentrations relevées dans l'air ambiant aux Etats-Unis et en Europe vont de non décelable à 0,4 µg/m³. Dans les cours d'eau européens, la concentration va de non décelable à 2,2 µg/litre.

Le 1,2,3-trichloropropane ne subit guère de transformation sous l'action de processus abiotiques (par

exemple, attaque par les radicaux hydroxyle engendrés par voie photochimique) et il pourrait donc persister pendant de longues durées. En revanche, il peut être éliminé des systèmes aquatiques par évaporation et passer du sol aux eaux souterraines par lessivage, en raison de la valeur peu élevée de son coefficient de sorption aux particules du sol (K_{oc}). Il est difficilement biodégradable et ne se transforme que lentement, en aérobiose ou en anaérobiose, sous l'action des bactéries. Les données relatives à la bioconcentration de cet alcane chloré montrent qu'il ne manifeste probablement pas de tendance à la bioaccumulation.

Les principales voies d'exposition au 1,2,3-trichloropropane sont l'inhalation d'air contaminé ou l'ingestion d'eau de boisson polluée. Il peut être absorbé par voie transcutanée, mais dans une proportion plus limitée.

L'expérimentation animale montre que le 1,2,3-trichloropropane est rapidement résorbé dans les voies digestives, puis tout aussi rapidement métabolisé et excrété. C'est ainsi qu'une dose administrée par voie orale est excrétée en 60 h dans les urines (à hauteur de 50 à 65 %), dans les matières fécales (à hauteur de 15 à 20 %) et dans l'air inhalé sous forme de dioxyde de carbone (à hauteur de 20 %). La métabolisation du composé se révèle plus rapide chez la souris que chez le rat.

Après administration par voie orale à des rats, le principal métabolite urinaire (correspondant à 40 % de la radioactivité urinaire) identifié au bout de 6 h est un conjugué avec l'acide mercapturique, la *N*-acétyl-*S*-(3-chloro-2-hydroxypropyl)-*L*-cystéine. Dans les urines de 24 heures, on trouve un second métabolite, qui est un conjugué avec la cystéine, à savoir la *S*-(3-chloro-2-hydroxypropyl)-*L*-cystéine. Soixante heures après administration par voie orale de [¹⁴C]-1,2,3-trichloropropane, la radioactivité due au carbone-14 est encore présente dans les organes cibles (comme le foie, le rein et l'estomac antérieur [portion aglandulaire]). Après injection intraveineuse de 1,2,3-trichloropropane à des rats, l'un des principaux métabolites retrouvés dans la bile s'est révélé être l'acide 2-(*S*-glutathionyl)malonique. Chez la souris, le spectre métabolique est plus complexe.

L'isolement de ces métabolites incite à penser que la biotransformation du 1,2,3-trichloropropane comporte une conjugaison avec le glutathion (GSH) et une oxydation. On a suggéré une voie hépatique comportant une oxygénation, catalysée par les oxydases à fonction mixte, au niveau d'un carbone terminal pour donner une chlorhydrine, après quoi d'autres réactions conduiraient à la formation des métabolites observés. Une deuxième voie métabolique intrahépatique pourrait faire intervenir la formation, catalysée par la GSH-transférase, de conjugués avec le glutathion, qui subiraient ensuite

encore une biotransformation intrahépatique ou passeraient dans la bile ou le plasma.

La toxicité aiguë du 1,2,3-trichloropropane est modérée, avec une valeur de la DL₅₀ qui va de 150 à 500 mg par kg de poids corporel chez le rat. Par voie cutanée, la toxicité est moindre, la seule étude dont on dispose chez le rat faisant état d'une DL₅₀ de 836 mg/kg de poids corporel. Chez le lapin, la valeur de la DL₅₀ par voie cutanée est comprise entre 384 et 2457 mg/kg de poids corporel. En ce qui concerne l'exposition dans l'air, on a obtenu une CL₅₀ à 4 h d'environ 3000 mg/m³ chez le rat et la souris. L'effet toxique le plus marqué consiste en une irritation de la muqueuse oculaire et nasale ainsi qu'en lésions hépatiques et rénales.

Le 1,2,3-trichloropropane a un effet irritant sur la peau et les muqueuses. Les divers tests effectués sur des cobayes montre que le 1,2,3-trichloropropane n'a aucun effet sensibilisateur ou du moins un effet minime.

Le principal effet constaté chez des rats F344 et des souris B6C3F1 après des expositions répétées par la voie respiratoire à des doses de 1,2,3-trichloropropane allant jusqu'à 780 mg par m³ pendant 9 jours, a été une dégénérescence et une atteinte inflammatoire microscopiques au niveau de la muqueuse olfactive nasale. Chez la souris, le poids des testicules était sensiblement réduit à la dose la plus élevée, mais sans que l'on puisse observer d'anomalies histologiques. On n'a pas observé d'autres anomalies si ce n'est une modification du poids du foie dans le groupe exposé à la dose la plus forte. Lors d'une expérience comportant l'exposition répétée de rats et de souris à des doses allant jusqu'à 61 mg/m³, la dose sans effet nocif général observable (NOAEL) a été trouvée égale à 6 mg/m³ pour le rat et à 18 mg/m³ pour la souris, l'effet en question étant une modification de l'épithélium olfactif décelable par examen histologique.

Au cours d'une autre étude pendant laquelle des rats CD ont été exposés durant 13 semaines à des doses allant jusqu'à 300 mg/m³, on a observé des effets toxiques au niveau des voies respiratoires, des poumons et du foie. Une étude longitudinale comportant l'exposition à des doses allant jusqu'à 9,2 mg/m³ a révélé des signes d'irritation des muqueuses (augmentation de la lacrimation), même à la dose la plus faible (3,1 mg/m³). Les seuls effets généraux observés consistaient en anomalies hématologiques et en une augmentation du poids du poumon et des ovaires, mais sans anomalies histologiques correspondantes.

Après avoir administré du 1,2,3-trichloropropane par voie orale à des rats F344 pendant des périodes de durée moyenne, les principales lésions imputables à la toxicité de ce composé ont été observées au niveau du

foie, du rein et des fosses nasales, les mâles présentant une plus grande sensibilité à cet égard. Les anomalies hématologiques relevées à des doses journalières supérieures ou égales à 16 mg par kg de poids corporel ont été interprétées comme traduisant une anémie non régénérative, peut-être liée à une dépression de l'érythro-poïèse. Une étude de 17 semaines pendant lesquelles des rats ont reçu le composé par gavage a permis d'obtenir, pour la dose la plus faible produisant un effet observable (LOAEL), la valeur de 8 mg/kg p.c. par jour dans le cas des mâles et de 16 mg/kg p.c. par jour dans le cas des femelles (augmentation du poids absolu du foie). Chez la souris B6C3F1, les principaux organes cibles de l'action toxique sont le poumon, le foie et l'estomac antérieur. La souris supporte des doses plus élevées que le rat, la LOAEL (hyperplasie de l'épithélium bronchiolaire ou hyperplasie et hyperkératose de l'estomac antérieur) étant de 63 mg/kg p.c. par jour pour la souris femelle et de 125 mg/kg p.c. par jour pour la souris mâle. L'effet cardiotoxique évoqué par un groupe de travail n'est pas confirmé par ces études, qui comportaient une durée d'administration du produit comparable, voire plus longue. Lorsque le gavage consistait dans l'administration d'un bolus, il a déterminé des effets plus graves que l'administration en continu dans l'eau de boisson à dose comparable. En administrant du 1,2,3-trichloropropane à des rats Sprague-Dawley dans leur eau de boisson pendant 13 semaines, on a obtenu pour la LOAEL (effet retenu : augmentation du poids relatif du foie et du rein) la valeur de 17,6 mg/kg p.c. par jour pour les femelles et de 113 mg/kg p.c. par jour pour les mâles.

Divers tests de génotoxicité *in vitro* (par exemple, des mutations géniques dans des cellules bactériennes ou mammaliennes, des conversions géniques chez *Saccharomyces cerevisiae*, des échanges entre chromatides soeurs, des aberrations chromosomiques et la formation de micronoyaux) indiquent à l'évidence que le 1,2,3-trichloropropane peut être génotoxique en présence d'un système d'activation métabolique. Les données isolées relatives à une action génotoxique directe du composé paraissent en revanche discutables. *In vivo*, l'élué en milieu alcalin permet de déceler des ruptures monocaténares de l'ADN, mais une épreuve de létalité dominante n'a pas permis de mettre la génotoxicité du composé en évidence.

Le principal adduit avec l'ADN est le S-[1-(hydroxyméthyl)-2-(N⁷-guanyl)éthyl]glutathion, mais d'autres adduits avec l'ADN ont été mis en évidence dans des lésions préneoplasiques et néoplasiques affectant les organes cibles.

Les résultats d'une étude portant sur deux générations de souris Swiss montrent que le 1,2,3-trichloropropane réduit la fécondité et perturbe la fonction de reproduction à la dose de 120 mg/kg p.c. par jour

(administrée par gavage), tant dans la génération parentale que dans la progéniture, avec une toxicité générale qui reste cependant peu marquée. Un essai comportant des accouplements croisés a permis, semble-t-il, de montrer que la toxicité pour l'appareil reproducteur était plus marquée chez les femelles que chez les mâles. Chez toutes les femelles de la génération F₁ exposées au 1,2,3-trichloropropane, la durée moyenne du cycle oestral était sensiblement augmentée, la dose la plus faible produisant cet effet étant égale à 30 mg/kg p.c. par jour.

Le 1,2,3-trichloropropane est un cancérigène à localisations multiples provoquant des lésions préneoplasiques correspondantes chez le rat et la souris après administration prolongée par gavage. Les principales cibles de son action cancérigène sont l'estomac antérieur ainsi que la muqueuse buccale chez les rats des deux sexes, la glande mammaire chez les femelles, le rein et le pancréas chez les mâles ainsi que la glande préputiale et la glande clitoridienne qui sont des organes homologues chez le mâle et la femelle. Chez la souris, la réaction au traitement par le 1,2,3-trichloropropane se traduit par des néoplasmes de l'estomac antérieur, du foie et de la glande de Harder. On a également signalé des tumeurs de nature inhabituelle, comme des carcinomes de la glande de Zymbal et des polypes adénomateux ou des adénocarcinomes de l'intestin chez le rat ainsi que des cancers de l'utérus chez la souris. Compte tenu de l'incidence très élevée des néoplasmes de l'estomac antérieur dans les groupes de rats (33 à 66 %) et de souris (près de 100 %) soumis à des doses peu élevées, cette activité cancérigène aurait pu être décelée même à plus faible dose et la LOAEL correspondant à une augmentation significative de l'incidence tumorale est largement inférieure à 3 mg/kg p.c. par jour chez le rat et à 6 mg/kg p.c. par jour chez la souris.

Le 1,2,3-trichloropropane est cancérigène pour le rat et la souris et entraîne l'apparition de tumeurs très variées chez les animaux des deux sexes. Les données relatives à son mode d'action, et notamment les études sur son métabolisme, sa génotoxicité et la formation d'adduits avec l'ADN incitent à penser que le mécanisme de cancérisation comporte l'interaction directe entre un métabolite actif et le matériel génétique. L'exposition au 1,2,3-trichloropropane doit donc être évitée.

On a procédé à une caractérisation du risque selon les directives de la Commission européenne qui portait sur l'environnement aquatique et qui a consisté à calculer le rapport de la concentration environnementale locale prédite (PEC), basée sur des mesures, à la concentration environnementale correspondante prédite sans effet (PNEC).

La PNEC pour les eaux de surface a été déterminée à partir de la valeur la plus faible de la CE₅₀ tirée de tests en systèmes fermés afin de réduire au minimum les pertes de 1,2,3-trichloropropane. Pour obtenir la PNEC, on a utilisé la valeur de la CE₅₀ à 48 h pour l'immobilisation de *Daphnia magna* (20 mg/litre) et on a appliqué au dénominateur un facteur d'incertitude de 1000 : PNEC = 20 mg/litre ÷ 1000 = 0,02 mg/litre. Bien qu'une valeur plus faible ait été obtenue pour *Ceriodaphnia cf. dubia* (CE₅₀ à 48 h de 4,1 mg/litre), le test correspondant n'était basé que sur les concentrations nominales et n'a donc pas été utilisé pour la caractérisation du risque.

En prenant comme PEC la concentration la plus récemment déterminée du 1,2,3-trichloropropane dans les eaux de surface (soit 2,2 µg/litre), on trouve pour le quotient de dangerosité (PEC/PNEC) la valeur suivante : 2,2 µg/litre ÷ 0,02 µg/litre = 110. Comme ce chiffre est inférieur à 1, il n'est pas nécessaire d'obtenir d'autres données, de pratiquer d'autres tests ou de prendre des mesures de réduction du risque.

On n'a pas trouvé de données relatives aux effets toxiques de ce composé chimique sur les invertébrés terrestres ou les plantes supérieures. En ce qui concerne l'environnement terrestre, les études toxicologiques dont on dispose pour mesurer l'inhibition de l'activité microbienne terricole par le 1,2,3-trichloropropane ne peuvent pas être considérées comme suffisantes en vue d'une caractérisation quantitative du risque.

RESUMEN DE ORIENTACIÓN

El presente CICAD sobre el 1,2,3-tricloropropano, preparado por el Instituto Fraunhofer de Toxicología y de Investigación sobre los Aerosoles (Alemania), se basa en informes compilados por el Comité Consultivo Alemán sobre las Sustancias Químicas Importantes para el Medio Ambiente (BUA, 1993) y la Comisión Alemana de Investigación de los Peligros para la Salud de las Sustancias Químicas en el Entorno de Trabajo (MAK, 1993). En noviembre de 2001 se realizó una búsqueda bibliográfica amplia de bases de datos pertinentes para los efectos en la salud y en septiembre de 2002 para los efectos en el medio ambiente, a fin de localizar cualquier referencia de interés publicada después de las incorporadas a estos informes. La información relativa a la preparación y el examen colegiado de los documentos originales figura en el Apéndice 1. La información sobre el examen colegiado de este CICAD se presenta en el Apéndice 2. Este CICAD se aprobó en una reunión de la Junta de Evaluación Final celebrada en Monks Wood (Reino Unido) del 16 al 19 de septiembre de 2002. La lista de participantes en la Junta de Evaluación Final figura en el Apéndice 3. También se reproduce en este documento la Ficha internacional de seguridad química (ICSC 0683) para el 1,2,3-tricloropropano, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1999).

El 1,2,3-tricloropropano (CAS N° 96-18-4) es un alcano clorado. No sólo se fabrica como tal, sino que también se obtienen cantidades significativas como subproducto de la producción de otros compuestos clorados, entre ellos la epíclorohidrina. Se utiliza como intermediario en la síntesis de otros productos químicos (por ejemplo, plaguicidas) y como agente de formación de enlaces en la producción de polímeros, por ejemplo polisulfuros y hexafluoropropileno. En informes más antiguos se identificaba el 1,2,3-tricloropropano como disolvente de compuestos hidrófobos y resinas, como limpiador de pinturas y barnices y como agente desengrasante.

El compartimento destinatario más importante del 1,2,3-tricloropropano en el medio ambiente es el aire (alrededor del 85%), seguido del agua (en torno al 11%). En los Estados Unidos y Europa se han notificado concentraciones de 1,2,3-tricloropropano en el aire ambiente que oscilan entre valores no detectados y $0,4 \mu\text{g}/\text{m}^3$. En los ríos de Europa, las concentraciones varían entre valores no detectados y $2,2 \mu\text{g}/\text{l}$.

El 1,2,3-tricloropropano liberado en el medio ambiente apenas se degrada por procesos abióticos (por ejemplo, transformación mediante radicales hidroxilo

producidos por vía fotoquímica), por lo que podría mantenerse presente durante períodos prolongados. Sin embargo, se puede eliminar de los sistemas acuáticos por evaporación y podría sufrir un proceso de lixiviación del suelo hacia el agua freática, debido a los bajos coeficientes de sorción en el suelo (K_{oc}) notificados para este compuesto. No se degrada con facilidad y las bacterias lo transforman sólo lentamente en condiciones aerobias y anaerobias. Los datos disponibles sobre este alcano clorado indican que no es probable su bioacumulación.

Las vías principales de exposición al 1,2,3-tricloropropano son la inhalación de aire contaminado y el consumo de agua de bebida contaminada. Se puede absorber por vía cutánea en una medida más limitada.

En estudios con animales, el 1,2,3-tricloropropano se absorbe con rapidez del tracto gastrointestinal, se metaboliza y se excreta. Tras la administración oral, se excretó en un plazo de 60 horas por vía urinaria (50-65%), fecal (15-20%) y respiratoria como anhídrido carbónico (20%). Parece que los ratones metabolizan el 1,2,3-tricloropropano con mayor rapidez que las ratas.

Tras la administración oral a ratas, el principal metabolito urinario (40% de radioactividad urinaria) identificado después de seis horas fue un conjugado del ácido mercaptúrico, la *N*-acetil-*S*-(3-cloro-2-hidroxipropil)-*L*-cisteína. En la orina de 24 horas se detectó un segundo metabolito, un conjugado de la cisteína (*S*-(3-cloro-2-hidroxipropil)-*L*-cisteína). Incluso 60 horas después de la administración oral de [^{14}C]1,2,3-tricloropropano se observó actividad del ^{14}C en los órganos destinatarios (es decir, el hígado, el riñón y la región cardíaca del estómago). Tras la administración intravenosa de 1,2,3-tricloropropano a ratas, un metabolito importante en la bilis fue el ácido 2-(*S*-glutathionil)-malónico. En ratones, el espectro de los metabolitos urinarios es más complejo.

El aislamiento de los metabolitos antes mencionados parece indicar que en la biotransformación participan tanto la conjugación con el glutatión como la oxidación. Una vía propuesta en el hígado es la oxigenación de un carbono terminal del 1,2,3-tricloropropano catalizada por una oxidasa de función mixta para producir una clorohidrina, seguida de otras reacciones que dan lugar a la formación de los metabolitos observados. Una segunda vía en el hígado puede ser la formación de conjugados del glutatión por acción de la glutatión transferasa, que luego sufren una nueva biotransformación en el hígado o se excretan en la bilis o el plasma.

El 1,2,3-tricloropropano tiene una toxicidad aguda moderada, con valores de la DL_{50} en ratas comprendidos entre 150 y 500 mg/kg de peso corporal. La toxicidad

cutánea es más baja, con valores notificados de la DL₅₀ de 836 mg/kg de peso corporal al día de un estudio único con ratas y valores comprendidos entre 384 y 2457 mg/kg de peso corporal en conejos. En ratas y ratones se obtuvo un valor de la CL₅₀ a las cuatro horas de unos 3000 mg de 1,2,3-tricloropropano/m³. El efecto tóxico más llamativo es la irritación de la mucosa ocular y nasal y lesiones hepáticas y renales.

El 1,2,3-tricloropropano irrita la piel y las membranas mucosas. En diversas pruebas con cobayas, se observó un efecto sensibilizador nulo o sólo muy ligero.

El efecto primordial de la exposición repetida de ratas F344 y ratones B6C3F1 por inhalación a concentraciones de hasta 780 mg de 1,2,3-tricloropropano/m³ durante nueve días fue un cambio degenerativo e inflamatorio microscópico en la mucosa olfativa nasal. En ratones, se observó una disminución importante del peso de los testículos con la dosis más alta, pero sin cambios histopatológicos asociados. No aparecieron otros fenómenos, salvo cambios en el peso del hígado en el grupo con la dosificación más alta. En un experimento con dosis repetidas de hasta 61 mg/m³, la concentración general sin efectos adversos observados (NOAEL) para los cambios detectables por examen histopatológico en el epitelio olfativo fue de 6 mg/m³ en las ratas y de 18 mg/m³ en los ratones.

En otro estudio en el que se expusieron ratas CD a concentraciones de hasta 300 mg/m³ durante 13 semanas, se observaron efectos tóxicos en las vías respiratorias superiores, los pulmones y el hígado. En un estudio complementario con dosis de hasta 9,2 mg/m³ se notificaron signos de irritación de las membranas mucosas (aumento de la descarga lacrimal), incluso con la concentración mínima de 3,1 mg/m³. Los únicos efectos sistémicos detectados fueron cambios en los parámetros hematológicos y un aumento de peso de los pulmones y los ovarios, sin las observaciones microscópicas correspondientes.

Tras una exposición oral de duración media de ratas F344 al 1,2,3-tricloropropano, las principales lesiones tóxicas se produjeron en el hígado, el riñón y los turbinatos nasales, mostrando mayor sensibilidad los machos. Los cambios hematológicos con 16 mg/kg de peso corporal al día y dosis superiores se interpretaron como anemia no regenerativa, posiblemente asociada con una depresión de la eritropoyesis. La concentración más baja con efectos adversos observados (LOAEL) para un tratamiento de 17 semanas mediante sonda fue de 8 mg/kg de peso corporal al día en ratas macho y de 16 mg/kg de peso corporal al día en ratas hembra (aumento del peso absoluto del hígado). En ratones B6C3F1, los principales órganos destinatarios de la acción tóxica fueron los pulmones, el hígado y la región cardíaca del estómago. Los ratones toleraron dosis más

altas que las ratas, con valores de la LOAEL (hiperplasia del epitelio bronquiolar e hiperplasia e hiperqueratosis de la región cardíaca del estómago) de 63 mg/kg de peso corporal al día en ratas hembra y de 125 mg/kg de peso corporal al día en ratones macho. Un efecto cardiotoxico examinado por un grupo de trabajo no se confirmó en estos estudios, que abarcaron períodos de tratamiento comparables o más prolongados. La administración de un bolo mediante sonda produjo efectos más graves que la aplicación continua en el agua de bebida con una dosificación comparable. Cuando se administró a ratas Sprague-Dawley 1,2,3-tricloropropano con el agua de bebida durante 13 semanas, los valores de la LOAEL para el aumento relativo del peso del hígado y el riñón fueron de 17,6 mg/kg de peso corporal al día para las ratas hembra y de 113 mg/kg de peso corporal al día para las ratas macho.

En diversas pruebas de genotoxicidad *in vitro* (por ejemplo mutaciones de genes en bacterias y células de mamíferos, conversiones de genes en *Saccharomyces cerevisiae*, inducción del intercambio de cromátidas hermanas, aberraciones cromosómicas y micronúcleos) se puso de manifiesto un potencial genotóxico del 1,2,3-tricloropropano en presencia de sistemas de activación metabólica. Parecen cuestionables los datos aislados sobre una acción genotóxica directa del 1,2,3-tricloropropano. *In vivo* se detectaron roturas de cadenas sencillas de ADN mediante elución alcalina, mientras que no hubo acción genotóxica en una prueba de dominancia letal.

En lesiones preneoplásicas y neoplásicas de órganos destinatarios se identificó S-[1-(hidroximetil)-2-(N⁷-guanil)etil]glutatin, principal aducto de ADN, y otros aductos de ADN.

Los resultados de un estudio de dos generaciones con ratones suizos pusieron de manifiesto que el 1,2,3-tricloropropano alteraba la fecundidad y la reproducción con una dosis de 120 mg/kg de peso corporal al día (administrado mediante sonda) tanto en la generación parenteral como en las crías en presencia de una toxicidad sistémica sólo ligera. Un ensayo de apareamiento cruzado parecía indicar una mayor toxicidad para el sistema reproductivo de las hembras que de los machos. La duración media del ciclo estral fue notablemente más alta para todas las hembras de la generación F₁ expuestas al 1,2,3-tricloropropano, siendo la dosis más baja de 30 mg/kg de peso corporal al día.

El 1,2,3-tricloropropano es carcinogénico para diversos órganos, con las correspondientes lesiones preneoplásicas tanto en ratas como en ratones tras su administración prolongada mediante sonda. Los puntos principales de su acción carcinogénica son la región cardíaca del estómago y la mucosa oral en ratas de ambos sexos, la glándula mamaria en las ratas hembra y

el páncreas y el riñón en las ratas macho, así como las glándulas prepucial y clitorídea, como órganos homólogos en ratas macho y hembra, respectivamente. La reacción en los ratones fue de neoplasmas en la región cardíaca del estómago, el hígado y la glándula de Harder. Se notificaron tipos poco frecuentes de tumores, como carcinomas de la glándula de Zymbal y pólipos adenomatosos o adenocarcinomas del intestino en ratas y neoplasmas uterinos en ratones. Teniendo en cuenta la incidencia muy elevada de neoplasmas en la región cardíaca del estómago en grupos de ratas (33-66%) y ratones (casi el 100%) tratados con una dosis baja, esta actividad carcinogénica se podría haber detectado incluso con dosis más bajas, y la LOAEL para la incidencia de tumores significativamente elevada estará muy por encima de 3 mg/kg de peso corporal al día en ratas y 6 mg/kg de peso corporal al día en ratones.

El 1,2,3-tricloropropano es carcinogénico en ratas y ratones, induciendo una gran variedad de tumores en ambos sexos. Los datos sobre el mecanismo de acción, incluidos los estudios sobre el metabolismo, la genotoxicidad y la determinación de la formación de aductos del ADN, parecen indicar que en el mecanismo de inducción de tumores interviene la interacción directa de un metabolito activo con material genético. Por consiguiente, se debería evitar la exposición al 1,2,3-tricloropropano.

Se realizaron pruebas de toxicidad aguda del 1,2,3-tricloropropano utilizando diversas especies acuáticas de distintos niveles tróficos.

Se realizó una caracterización del riesgo de muestra conforme a la Comisión Europea con respecto al medio ambiente acuático, calculando la razón entre la concentración local prevista en el medio ambiente (PEC), basada en los datos medidos, y la correspondiente concentración prevista sin efectos (PNEC).

Se estimó una PNEC para el agua superficial a partir del valor más bajo de la CE_{50} obtenido en pruebas realizadas en sistemas cerrados para reducir al mínimo las pérdidas de 1,2,3-tricloropropano. Se utilizó la CL_{50} a las 48 horas para la inmovilización de *Daphnia magna* (20 mg/l) a fin de obtener la PNEC, junto con un factor de incertidumbre de 1000: $PNEC = 20 \text{ mg/l} \div 1000 = 0,02 \text{ mg/l}$. Aunque se obtuvo un valor más bajo para *Ceriodaphnia cf. dubia* (CE_{50} a los 48 horas de 4,1 mg/l), esta prueba sólo se basó en concentraciones nominales y, por consiguiente, no se utilizó en la caracterización del riesgo.

Utilizando la concentración más alta de 1,2,3-tricloropropano medida recientemente en el agua superficial (2,2 µg/l) como PEC, el cociente de peligro (PEC/PNEC) se convierte en $2,2 \text{ µg/l} \div 0,02 \text{ µg/l} = 110$.

Debido a que este valor es inferior a la unidad, no hay necesidad de ulterior información, pruebas o medidas de reducción del riesgo.

No se identificaron datos sobre los efectos tóxicos de este producto químico en invertebrados terrestres o en plantas superiores. Para el compartimento terrestre, los estudios de toxicidad disponibles, en los que se midió la inhibición por el 1,2,3-tricloropropano de la actividad microbiana ligada al suelo, no se pueden considerar suficientes para respaldar una caracterización cuantitativa del riesgo.

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